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RHEUMATOID ARTHRITIS ASSOCIATED WITH SPLENOMEGALY AND LEUKOPENIA*

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IN 1924, Felty[1] reported 5 cases of chronic arthritis in adults, with associated splenomegaly and leukopenia. The patients ranged from forty-five to sixty-five years of age and included 3 men and 2 women. All had experienced marked weight loss. Two had low-grade pyrexia. All showed a yellowish-brown pigmentation of the skin, usually confined to the exposed surfaces. Three patients exhibited enlarged lymph nodes, but none hepatomegaly. The arthritis was neither widespread nor severe. Roentgenograms in 3 cases revealed "infectious arthritis"; in another, no articular changes were noted. Leukopenia, with white-cell counts varying from 1000 to 4200, was a striking feature in each case. Four of the 5 patients had a mild secondary anemia. Felty suggested either that the triad represented a pathologic process caused by a noxa that concurrently affected the spleen, blood and joints or that the splenomegaly and leukopenia were entirely unrelated to the arthritis. Unfortunately, no pathological studies were obtained. Since this communication, a number of reports relating to patients with arthritis, splenomegaly and leukopenia have appeared; most of them have been referred to as cases of Felty's syndrome.

Having encountered this triad from time to time during the last thirteen years, we wish to place on record some of our observations. We shall first present the clinical data and autopsy findings of a case very similar to those described by Felty. We shall next attempt a critical analysis of this syndrome based on our clinical experience and a review of the pertinent literature, as well as to point out the various pitfalls that may be encountered if the term "Felty's syndrome" is used indiscriminately. Finally, we shall present our reasons for rejecting this term and for retaining the more accurate designation, rheumatoid arthritis.

CASE 1. Mrs. J. K. (M.G.H. 132442), a 64-year-old woman, entered the hospital because of failing vision during the previous 3 months. For at least 20 years, she had had arthritis involving primarily the hands, knees, feet and spine. Constitutional symptoms had been moderate except for marked weight loss. Pallor was first noted 1 year before entry, and anorexia had been present for 6 months. Five years previously, diabetes mellitus was discovered, and dietary treatment without insulin prescribed.

At the time of admission, the patient was afebrile and presented no evidence of infection. The positive physical findings were pallor, signs of weight loss, brown pigmentation of the shins and of the dorsums of the feet, bilateral immature cataracts, pulmonary emphysema, an enlarged spleen (the edge being palpable 3 fingerbreadths below the left costal margin), a palpable liver edge (2 fingerbreadths below the right costal margin) and slight enlargement of the cervical and left inguinal lymph nodes. The blood pressure was 130/60. Examination of the joints showed swelling and deformity of the articulations of the hands and fingers, with ulnar deviation of the latter. Permanent flexion of all the metacarpophalangeal joints and inability to make a fist with either hand were readily evident. The knees and ankles were swollen, the former being flexed; both showed limitation of motion. The toes were painful, and their motions restricted. The neck was held stiffly, and full motion of the cervical spine was impossible. The motions of the dorsal and lumbar spine were limited and painful. Subcutaneous nodules were not demonstrable.

Examination of the blood disclosed a persistent leukopenia, the white-cell count varying from 1500 to 4300. The differential count on admission, when the white-cell count was 1600, was: 59 per cent neutrophils, 36 per cent lymphocytes, 2 per cent monocytes and 3 per cent eosinophils. The erythrocyte count of 2,800,000, and the hemoglobin of 49 per cent (Sahli) at the time of entry rose after transfusion therapy, which was without effect on the white cells. Gastric analysis revealed the absence of free hydrochloric acid after histamine administration. The

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stools did not contain occult blood. The diagnosis of a primary blood disease could not be established. Roentgenologic examination showed marked narrowing of the knee joints, second and third metacarpophalangeal articulations and both wrists. Bony atrophy was prominent. The knees also showed subluxation and extensive marginal proliferation, with spur formation at the tendon attachments. The gastrointestinal and genitourinary tracts were normal radiologically. Attempts to demonstrate esophageal varices failed. Catheterized urine specimens at the time of admission showed the presence of a trace of albumin and 10 to 15 erythrocytes and occasional coarse granular casts per high-power field. Blood cultures were sterile.

The diabetes was readily controlled with dietary measures and supplementary insulin therapy. On the 3rd hospital day, the patient developed fever and pyuria. Urine cultures made 2 days later showed *Escherichia coli*. During the next few weeks, there appeared multiple decubiti, otitis media and endophthalmitis of the left eye, which finally required enucleation. The patient failed progressively, and died on the 38th hospital day.

Autopsy (14 hours post mortem).* In addition to the anticipated urinary-tract, aural and skin infections, the following positive findings were observed.

Culture of the heart's blood showed *Esch. coli*. The liver weighed 1900 gm. and showed parenchymal-cell destruction, many gas bubbles and large clumps of bacilli. There was a comparatively slight neutrophilic reaction. The vertebral bone marrow showed a slight decrease in the number of fat cells, apparently because of a moderate hyperplasia of the red-cell elements, with large numbers of normoblasts and a fair number of megaloblasts. Although there were many mature polymorphonuclear cells, only occasional myelocytes were seen. The normal architecture of the lymph nodes was obscured by marked vascular engorgement and the complete absence of germinal centers. The sinuses were dilated and filled with erythrocytes, lymphocytes and monocytes; some of the last were large and contained phagocytized red cells. The pulp consisted of mature lymphocytes, was extremely vascular, and contained hemosiderin deposits. The spleen was enlarged, weighing 675 gm. On the surface, there was a white, firm, fibrotic area measuring 2.5 by 8.0 cm., interpreted as an old infarct. The normal architecture was indistinct, and the widely dilated sinusoids contained clumps of bacilli. The pulp was composed mostly of many polymorphonuclear cells, large mononuclear cells, erythrocytes and plasma cells. There were also occasional large phagocytes containing red blood cells.

Sections through the articulating surfaces of the patella and femur of one knee joint showed fibrous-tissue ankylosis, destruction of the articular cartilage and its replacement by dense fibrous tissue. Partial obliteration of the joint cavity had taken place, with the formation of smaller cavities lined by a thin layer of synovial cells. The synovial tissues exhibited slight lymphocytic infiltration and contained large pigment-filled phagocytes. The remaining cartilage was chiefly fibrous. The subchondral plate was interrupted in some places, and in many of these areas, the proliferating fibrous tissue had invaded the subchondral marrow spaces. Below the femoral articular surface, there was a large island of degenerating cartilage surrounded by bone trabeculae. A similar island of cartilage was found buried in the patella. All the bony structures showed moderate atrophy. The articular changes described were those of late and relatively inactive rheumatoid arthritis.

The anatomic diagnoses were as follows: rheumatoid arthritis, generalized; septicemia (*Esch. coli*); otitis media, bilateral, acute; mastoiditis, bilateral; pleuritis, chronic fibrous; pulmonary tuberculosis, right apical, healed; pulmonary infarcts, right lower lobe, with healing; bronchopneumonia; hepatitis, acute, with necrosis; splenomegaly (nonspecific); splenic infarct, healed; pyelonephritis, bilateral, acute and chronic; cystitis, acute; and lymphadenitis, chronic nonspecific.

Although the post-mortem findings in this case indicated sepsis as the chief cause of many of the changes observed, it should be emphasized that the triad of rheumatoid arthritis, splenomegaly and leukopenia was present before clinical evidence of urinary sepsis was obtained.

Except for the terminal septicemia, this case was similar to those described by Felty. The clinical course was characteristic of rheumatoid arthritis, a diagnosis that was readily confirmed by histologic examination. Were the splenomegaly and persistent leukopenia expressions of the same disease or of a concurrent malady? It seems reasonable to assume that the leukopenia was a manifestation of rheumatoid arthritis. However, since splenomegaly is not uncommon in patients with chronic pyelonephritis,[2] the changes in the spleen may have been due, at least in part, to the pyelonephritis, which obviously antedated the clinical evidence of its presence.

The following are a few brief case histories that illustrate even more clearly that the simultaneous occurrence of rheumatoid arthritis and one of a number of diseases may produce a clinical picture like that described by Felty.

CASE 2. Miss C. W. (M.G.H. 20050), a 40-year-old woman, entered the hospital in February, 1940, because of gastric symptoms. A large gastric ulcer was demonstrated by x-ray examination. The patient readily became symptom free when placed on an ulcer regime. She stated that she had suffered from a severe progressive arthritis for 8 years. Further examination and studies revealed, in addition to the crippling rheumatoid arthritis, a slight generalized lymphadenopathy, a splenomegaly, a persistent leukopenia (white-cell counts varying from 3800 to 4000) and a mild hypochromic anemia, characteristic findings that some have termed Felty's syndrome. It was soon established that the splenomegaly and leukopenia were secondary to hepatic disease caused by cinchophen ingestion 6 years previously. In March, 1941, the patient died from generalized peritonitis following perforation of the gastric ulcer.

Autopsy. Examination confirmed the suspected cause of death and proved the presence of a healed acute yellow atrophy of the liver, chronic congestive splenomegaly with fibrosis, and rheumatoid arthritis.

CASE 3. Mrs. F. B. (M.G.H. 326626), a 67-year-old woman, was first seen in 1933. She had had moderately severe arthritis since 1931. When examined, she showed

*We are indebted to Drs. Granville A. Bennett and Tracy B. Mallory for the report of the pathological findings.

the clinical picture and roentgenographic findings of fairly widespread rheumatoid arthritis. The spleen was readily palpable, and a leukopenia averaging about 3800 and a moderate hypochromic anemia were present. That these clinical findings were due to more than rheumatoid arthritis was suggested in 1934, when the patient expired suddenly because of a massive hematemesis.

Unfortunately, permission for a post-mortem examination was not obtained. It was therefore impossible to exclude cirrhosis of the liver with esophageal varices as the cause not only of the fatal hemorrhage but also of the splenomegaly and leukopenia.

CASE 4. Mrs. E. S. (M.G.H. 32491), a 22-year-old woman, presented herself in December, 1940, because of apparent rheumatoid arthritis of 18 months' duration. Splenomegaly, moderate normochromic anemia, slight leukopenia and generalized lymphadenopathy were present. Further search revealed that the splenomegaly and anemia were of at least 11 years' duration, having been noted while the patient was under observation for rheumatic heart disease. Subsequent investigation established the diagnosis of familial hemolytic anemia, and splenectomy was successfully performed.

CASE 5. Mrs. F. K. (M.G.H. 338331), a 32-year-old woman, presented the picture of rheumatoid arthritis, generalized adenopathy, splenomegaly, leukopenia and slight hypochromic anemia when first seen. However, at subsequent examination, 4 years later, the spleen was no longer palpable and the leukopenia had vanished, and yet the arthritis had progressed somewhat in severity.

In view of these illuminating personal experiences, it seemed worth while to review the literature since 1924 to determine whether the reported cases corresponded to those described by Felty or represented rheumatoid arthritis in association with another disease.

It hardly seems just to attribute the origin of the confusing eponym, "Felty's syndrome," to the observer who first drew attention to this triad. Felty[1] clearly indicated that splenomegaly and leukopenia were known to occur in patients with arthritis but believed it unusual for all three to occur together. Although he stated that "one is more or less forced to the conclusion that the syndrome is a distinct clinical entity, of which the outstanding symptoms are those related to the joints, and the outstanding signs are the enlarged spleen and the blood picture," he did not imply that the articular disturbance was a segregated or unusual joint disease, and he carefully considered the necessity for the elimination of other concurrent pathologic lesions.

The origin of the term, "Felty's syndrome," must be directly attributed to Hanrahan and Miller,[3] who so classified their case in 1932. Their patient, in addition to the triad of rheumatoid arthritis, splenomegaly and leukopenia, complained of belching and upper abdominal pain. The findings of hepatomegaly, urobilinuria, melena and anemia of the macrocytic type strongly suggest the existence of an accompanying disease, such as cirrhosis of the liver, although histologic examination of the spleen after its removal revealed nothing specific.

Another illustration of possible hepatic disease occurring in a patient with articular manifestations and giving a clinical picture resembling Felty's cases was reported by Craven[4] in 1934. This patient also had hepatomegaly and evidence of liver damage as measured by the bromsulfalein test of liver function. Sections of the spleen removed from this case were essentially the same as those reported by Hanrahan and Miller.[3]

Chronic gouty arthritis can on occasions clinically simulate rheumatoid arthritis.[5] In the case reported by Fitz,[6] a history of sudden recurring attacks of "rheumatism" eventually involving most of the joints, an elevated blood uric acid level and roentgenographic changes in certain of the smaller joints suggest that this patient may have had gouty arthritis. It is interesting to note von Jaksch's[7] case report in 1908 of "arthritis urica" associated with splenomegaly and leukopenia, in which necropsy grossly confirmed the diagnosis of gouty arthritis. Unfortunately, no microscopic findings were reported.

In 1936, Reich[8] reported a case of Felty's syndrome in which the white-cell counts were 7200 and 5300 and in which the joints are not mentioned. In this twenty-one-year-old man with a history of "rheumatism" at the age of six and with an aortic diastolic murmur, fever, night sweats and eventual death, the possibility of subacute bacterial endocarditis or active rheumatic fever was not excluded.

It is interesting that some observers not only have accepted this syndrome as an entity but also have essayed a search for its specific etiology. Singer and Levy[9] considered this group a special form of sepsis lenta, believing *Streptococcus viridans* to be the causative agent. Unfortunately, their cases presented too many complicating factors to be clearly defined. *Str. viridans* was isolated from the blood of their first case, and the course of the patient's illness was consistent with subacute bacterial endocarditis with fever, generalized petechiae, anemia and, finally, cardiac failure. At autopsy, however, the heart valves were normal, and no source of the bacteremia was found. Their second patient ran a more acute course, with a severe pancytopenia, and the bacteriologic and post-mortem findings were similar to those described in the first case.

From the case report by Williams[10] in 1936, one cannot be sure of the exact type of joint disease, the picture being consistent with either a specific infectious or a rheumatoid arthritis. Unfortunately,

the autopsy was restricted to the chest and abdomen, so that the post-mortem diagnosis of hypertrophic arthritis was based on examination of the spine. Williams believed the mechanism responsible for the syndrome to be a primary blood dyscrasia, with secondary articular involvement. From the clinical description given, one may consider it a case of malignant neutropenia, with an associated arthritis of unknown type. This was borne out by bone-marrow studies revealing hyperplasia and maturation arrest of the neutrophilic series.

Curtis and Pollard[11] concluded that so-called "Felty's syndrome" was merely a chance variant of ordinary rheumatoid arthritis, since calf-muscle biopsies from 4 patients with rheumatoid arthritis showed a similar picture to those taken from 4 patients with rheumatoid arthritis associated with splenomegaly and leukopenia and from 4 with splenomegaly and leukocytosis. We believe that the relation of muscle histology to joint disease is not sufficiently established to permit conclusions to be drawn. It should also be pointed out that 2 cases in the group reported by these authors had too many complicating features to be acceptable as unequivocally similar to Felty's cases, and that the spleen in another showed amyloid deposits in the follicles.

Diffuse chronic septic splenitis and healed and caseating tubercles in the lung were found at autopsy in the case described by Price and Schoenfeld[12] in 1934. This raises the question of differentiating pulmonary tuberculosis from rheumatoid arthritis as the cause for the splenomegaly in this patient, who appeared clinically to fall into the category under discussion.

Collins's[13] conclusion that the clinical picture of the arthritis in his 2 cases did not differ from that of rheumatoid arthritis seems warranted. Pathological verification was not obtained.

Lack of adequate studies, before and after death, has been one of the primary difficulties encountered in the classification of cases reported as Felty's syndrome. However, the most exhaustive studies may fail to reveal the exact diagnosis. This was strikingly shown by Steinbrocker and Sesit[14] in their description of a patient who corresponded clinically to Felty's cases. Varied and complete studies, including two lymph-node biopsies, were nonrevealing, and yet histologic study of the spleen after death showed Hodgkin's disease associated with terminal miliary tubercles. The joints were not examined.

It is readily evident that 11 of 14 cases reported in the literature as examples of Felty's syndrome strongly suggest the possibility that the unassociated accompanying disease was responsible for the splenomegaly and leukopenia. As has been previously pointed out, the pitfalls encountered when this term is used indiscriminately are many. They are due, in great measure, to failure to exclude the existence of some concurrent disease responsible for the enlarged spleen and the leukopenia, as well as failure to realize that splenomegaly and leukopenia may be manifestations of rheumatoid arthritis.

The occurrence of splenomegaly and adenopathy in rheumatoid arthritis was first mentioned in 1896 by Chauffard and Ramond[15] in adults, and in 1897 by Still[16] in children. Since then, diverse figures for the incidence of splenomegaly have appeared: 6 per cent by Waterhouse,[17] 8 per cent by Freund,[18] 10 to 15 per cent by Dawson,[19] 21 per cent by Coates and Delicati[20] and 23 per cent by McCrae.[21] The frequency of lymphadenopathy in this disease has been variously reported as follows: Freund,[18] 19 per cent; Coates and Delicati,[20] 53 per cent; Waterhouse,[17] 96 per cent; and others who give no definite figures. These reported differences are probably due to varying assiduity in the search for lymph nodes and differences in criteria for denoting enlargement.

Although slight or moderate grades of leukopenia are not unusual in rheumatoid arthritis, severe neutropenia is rare.[22] According to Collins,[13] whose criteria for the upper limits of a definitely pathologic leukopenia are a while-cell count of 2000 or a neutrophil count of 1000, leukopenia occurs in less than 0.5 per cent of the cases. Incidentally, less than half the cases designated as Felty's syndrome fall within this strict definition. In our unselected series of 293 cases of rheumatoid arthritis, we have observed splenomegaly in 7 per cent, lymphadenopathy in 31 per cent and leukopenia consistently under 5000 in 1 per cent.

In view of these findings, there seems to be no need to assume that any combination of splenomegaly, adenopathy or leukopenia with rheumatoid arthritis represents a new pathologic entity. However, from the figures given, the triad of arthritis, splenomegaly and leukopenia is encountered very rarely. For this reason, numerous concurrent pathologic entities that may cause splenomegaly or leukopenia, or both, in patients with rheumatoid arthritis must be borne in mind. From our experience, the commoner maladies to be searched for are chronic liver disease (cirrhosis or healed acute yellow atrophy), pernicious anemia, leukemia, granulocytopenia, hemolytic anemia, amyloid disease, malignant lymphoma and various acute and chronic infections. In addition, lupus erythematosus disseminatus, dermatomyositis and periarteritis nodosa may present some or all of the features of arthritis, splenomegaly and

leukopenia, and must be considered in the differential diagnosis. We are fully aware of the bizarre and often unrecognizable picture presented by some of these conditions. It is a common experience that the condition may defy diagnosis until the truth is revealed at autopsy.

The evolution of the definition of the clinical entity, rheumatoid arthritis, has been beset with too many confusing partitions and the introduction of new terms to encourage their continuance. In Case 1, the articular disorder was obviously rheumatoid arthritis; the leukopenia was presumably a manifestation of the same disease. However, the splenomegaly, as noted above, may be attributed, at least in part, to the chronic pyelonephritis. Our experience and that of others show how often another disorder may be responsible for the splenomegaly and leukopenia observed in patients with rheumatoid arthritis. We therefore believe that the term "Felty's syndrome," which implies a separate pathologic entity, has no reasonable foundation and should be discarded. It is far more important to realize that rheumatoid arthritis is a generalized disease that may affect with varying frequency the lymph nodes, spleen, bone marrow and many other tissues besides the articular structures.

Summary

The clinical record and autopsy findings of a patient whose pathologic picture was similar to the cases described by Felty are presented, with evidence demonstrating the articular disorder to be rheumatoid arthritis. The leukopenia was presumably a manifestation of the same pathologic process, whereas the splenomegaly may have resulted from the arthritis, the chronic pyelonephritis, or both.

The incidence of leukopenia and splenomegaly in association with rheumatoid arthritis, as noted in our clinical experience and in the literature, is enumerated. It is obvious that this triad as an expression of rheumatoid arthritis is but rarely encountered. In fact, we have been unable to find any pathologically verified case in the literature or in our own clinical material in which an extraneous cause of the splenomegaly and the leukopenia can be definitely eliminated.

The inadvisability of using the term, "Felty's syndrome," is pointed out. In the rare case in which an extraneous cause of splenomegaly and leukopenia can be eliminated, one should employ the more accurate name, "rheumatoid arthritis," with associated splenomegaly and leukopenia.

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URINARY TYPHOID CARRIERS*

Report of a Case

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THE pyogenic faculty of the typhoid bacillus and the surgical complications of typhoid fever have been the subjects of medical reports and debate for many years. In 1898, Keen[1] published a study based on the analysis of 900 recorded cases in which he discussed the suppurative lesions caused by typhoid bacilli in nearly every organ of the body, including units of the gastrointestinal and genitourinary tracts. These two systems play the leading roles in the carrier state that is considered directly responsible for nearly half the cases of typhoid fever.

Just how frequently one of these systems becomes permanently involved is difficult to say; the bacteriology is a moot point in many of the cases reported in the literature. The records in Massachusetts[2] from 1937 to 1941 inclusive reveal that there were 405 cases of typhoid fever during that period. The patients were all followed very carefully, and 16 were found to be carriers, 1 being a urinary carrier. This is a much smaller proportion than that found in many other series, possibly because in Massachusetts a person is not classified as a carrier until he is proved to harbor the organism five or more months after his initial infection, and he is not placed on the carrier list until a year has elapsed. This rule avoids the inclusion of patients who excrete the organisms longer than usual during their convalescence. Addition of a name to the permanent carrier list excludes the patient from any occupation that involves the handling of food.

The persistent focus of typhoid infection that is responsible for the carrier state is centered in the gall bladder in most cases. Garbat,[3] in his excellent monograph, presents evidence that "liver carriers," that is, carriers with chronic infection in the hepatic ducts or liver tissue, as well as "true intestinal carriers," do occur. Undoubtedly, these types are extremely rare.

Dehler[4] is credited with being the first to suggest surgical treatment of the carrier state; his article was published in 1907. Since then, many patients have been subjected to surgery for this reason, the great majority for drainage or removal of an infected gall bladder. These operations should not be undertaken unless a duodenal drainage has been done and the culture of the bile found to be positive for *Eberthella typhosa*. The reason for this, of course, is to rule out liver and intestinal carriers. With this precaution, excellent results from the surgical approach may be expected. Over 30 cases in Massachusetts have thus been operated on during a period of several years, with complete success in all but 1. This failure may have been due to a blind pocket of infection in the cystic duct that was not completely removed at the level of its junction with the common duct, or to retained calculi in one of these structures.

Although urinary carriers are far less commonly encountered than fecal carriers, their potential danger to the community is individually greater. This is due to the infectiousness of the excreta (as high as 43,000,000 organisms per cubic centimeter have been recorded[3]), to the frequency of urination, and to the carelessness in the disposal of urine that seems quite innocuous. Considering that bacilluria in this disease is often found, it is surprising that permanent urinary carriers are not commoner. Garbat[3] estimates that 49 per cent of patients present organisms in their urine during convalescence, and believes that such organisms originate in the upper urinary tract in most cases. Of these cases of bacilluria, about 2.5 per cent remain positive for two or three months after the fever has subsided, presumably owing to the presence of renal areas of focal necrosis that discharge bacilli into the excretory passages of the kidney. A small number of this last group become the chronic urinary typhoid carriers, and may thus remain a menace to the health of the community for many years.

In most of the recorded cases of urinary-tract involvement, the carrier state has not received particular mention or emphasis, operation having been undertaken on ordinary surgical grounds for the drainage or removal of infected tissues. Whether the renal damage in such cases is a result of the typhoid infection, or whether the infection has seized on an organ already weakened by previous or concurrent disease, is a question still to be answered. Probably, both conditions occur, but present-day evidence favors the theory

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that the typhoid bacillus is generally the secondary invader. The value to the public health of the discovery of these urinary carriers is obvious, but one often fails to recognize the great importance to the individual of determining the reason for his condition. Whereas chronic infection of the gall bladder with the typhoid bacillus weakens or destroys no vital organ, a persistent typhoid bacilluria implies upper-urinary-tract infection, and many of these cases have serious renal lesions.[5-8] Thorough urologic study and appropriate treatment may well serve to correct both the disease and the carrier state, as in the following case.

Case Report

The patient (C. H. 41515), a 37-year-old truck driver, became ill in August, 1939, and was admitted to his local hospital the following month with the provisional diagnosis of typhoid fever. It was found that he had been living in a household with a previously discovered carrier, and it was assumed that he had acquired his infection from this source through the medium of food or water. Little could be learned of his clinical course except that he suffered from headache, abdominal cramps and persistent fever ranging between 100 and 103°F. Laboratory study revealed a positive Widal test and two negative stool cultures. Examination of the urine, carried out the day after admission, showed innumerable pus cells in the sediment; no other investigation was made. The nurse's notes state that at no time did the patient seem very ill, and after an apparently uneventful recovery he was discharged on October 28, 1939, about 6 weeks after admission.

Because cultures of mixed stool and urine specimens were still positive for typhoid bacteria a year later, the patient's name was added to the carrier list of the Massachusetts Department of Public Health, and further study was begun. Specimens of bile obtained through a duodenal tube at this time (November 1, 1940) were negative, but a urine culture was positive, and the Department of Public Health, with the consent of the patient, arranged for complete urologic examination.

Little could be learned from the record, for there was no history of any serious illness or injury or of any complaint referable to the urinary tract, except for an occasional indefinite pain in the back. There had been no dysuria, hematuria, increased frequency or nocturia. Physical examination showed the patient to be a thin but otherwise healthy man with no significant defects. Neither kidney was palpable, and there was no costovertebral tenderness. The external genitals were normal. Rectal examination revealed a small, firm, benign prostate, uniform in consistence. There was no thickening in either seminal-vesicle region.

Cystoscopy revealed an irritable bladder, which tolerated no more than 120 cc. of fluid. However, the mucosa, ureteral orifices, trigone and internal sphincter margin were normal in appearance. A No. 5 Fr. catheter was passed easily along the right ureter for 30 cm., and a clear, rhythmic drip was obtained, which later became blood tinged. On the left side, neither a No. 5 nor a No. 4 Fr. catheter could be advanced beyond 22 cm. Phenolphthalein given intravenously appeared in 2 minutes on the right side, and a 10-minute collection showed an excretion of 9 per cent of the dye in 20 cc. of urine. No determination of function could be made on the left, since only a few drops of urine were obtained. The bladder urine contained many pus cells, free and in clumps, and on culture *E. typhosa* was recovered. Urine from the right kidney was normal and showed no growth, whereas that from the left kidney was positive on culture for typhoid bacilli. A retrograde pyelogram revealed normal excretory passages on the right, but none of the opaque solution passed up the ureter on the left side beyond the point of obstruction, where an elliptical calculus was lodged (Fig. 1). In the left renal area, there was a

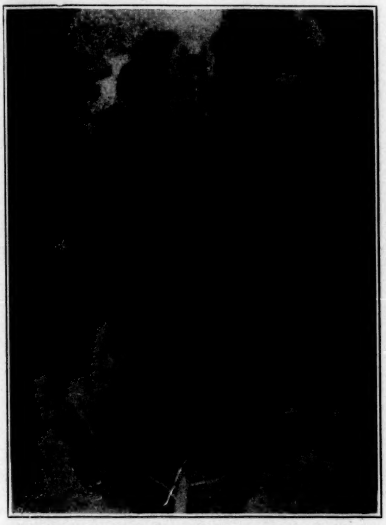

Figure 1. *Retrograde Pyelogram.*

The right side is normal, but there is a large calculus at the tip of the ureteral catheter on the left.

group of three small stones in the region of the lower pole of the kidney. Intravenous pyelograms again demonstrated good function on the right side, but there was very faint and delayed excretion of the dye on the left.

Two problems were thus presented: a badly damaged left kidney, as a result of ureteral obstruction and infection; and a typhoid-carrier state probably associated with this condition. After careful consideration of the medical and social aspects of the case, operation was decided on.

The patient re-entered the hospital on February 4, 1941. The interval history gave no new information. Physical examination showed no additional changes as compared with the earlier investigation, and an x-ray film showed the ureteral calculus to be in essentially the same position. Because of the rather long interval since the cystoscopic study, the bladder inspection was repeated, with exploration of the left ureter and intravenous injection of indigo carmine. The bladder was normal, and the dye appeared at the right ureteral orifice in good concentration in 4½ minutes. No dye appeared on the left side during the period of the observation, which was extended to 50 minutes. A No. 4 Fr. ureteral catheter was blocked at

essentially the same level as before, and there was no drip of urine. Another attempt at a left retrograde pyelogram was unsuccessful; there was still complete obstruction of the ureter by the stone. Culture of the bladder urine again showed *E. typhosa.* The white-cell and red-cell counts were 5900 and 4,300,000 respectively; the hemoglobin was 95 per cent; and the differential count showed 70 per cent polymorphonuclears, 28 per cent lymphocytes, and 2 per cent basophils. The blood Wassermann reaction was negative, as was a blood culture and a Widal test. Blood sugar, calcium, phosphorus and uric acid determinations were all normal.

Operation was performed on February 6. A left lumbar incision was made, with preservation of the 11th and 12th intercostal nerves. When the renal fossa was entered, a large, soft kidney was found, with surprisingly few inflammatory adhesions. The renal parenchyma was extremely thin as a result of the severe hydronephrosis. The calculi noted in the x-ray films could be palpated in the lower calyx and upper ureter. Because of the extreme destructive changes present in the kidney and because of the serious infection known to exist, it was decided that nephrectomy should be performed. This was easily accomplished after a small vascular pedicle was isolated. A few centimeters of the upper ureter, including the region of the impacted calculus, was removed with the specimen.

The pathological report was as follows:

> The specimen consists of a previously partially sectioned kidney weighing 120 gm. It measures 13 by 6 by 3 cm. There is an attached portion of the ureter, 8 cm. in length. When the incision is continued in the usual manner and the kidney divided into halves, the pelvis and calyxes are greatly dilated, so that there remains only a narrow rim of renal parenchyma, measuring 3 mm. around the periphery. The pelvis and calyxes are lined by glistening, gray, finely granular mucosa. Three stones are seen, the largest 0.4 cm. and having prongs on the surface. The ureter communicates with the pelvis and is markedly dilated, for the most part up to 2 cm. in circumference, but narrows suddenly to almost pinpoint size at the level where it is tied (Fig. 2).

Microscopic diagnosis: chronic pyelonephritis, hydronephrosis, hydroureter and nephrolithiasis. Cultures taken from the renal cavity and from the ureteral calculus showed *E. typhosa.*

The patient made an uneventful convalescence. A small amount of secondary wound infection at the posterior angle of the incision responded to drainage and the application of heat; culture of the pus failed to grow typhoid bacilli. The patient was discharged in good condition on March 2. He was seen 1 month and 2 months later in the Out-Patient Department, at which time he reported that he was feeling well and had no urinary complaints. Examination of the urine showed it to be normal except for 0 to 3 pus cells per high-power field in the sediment. The incision was dry and well healed.

Cultures of the bladder urine taken on the following dates were negative for typhoid infection: February 19 and 22; March 1, 10, 17, 24 and 27; May 5, 24 and 26;

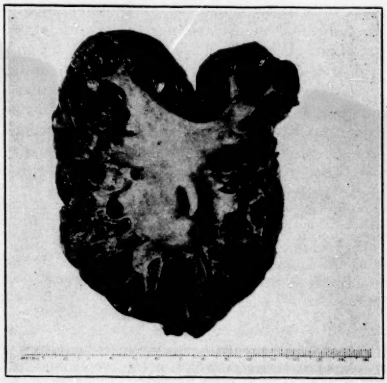

FIGURE 2. *Gross Specimen Sectioned Longitudinally. Note the thin rim of parenchyma at the periphery and the dilated pelvis and calyxes.*

and July 5. The patient's name was removed from the carrier list shortly after the last negative culture.

SUMMARY

The typhoid-carrier state in most cases is due to residual chronic infection in the gall bladder. In a small but important percentage of cases, the focus of infection is in the urinary tract.

All persons in this latter group should have complete urologic investigation, for many of them have serious renal lesions.

An illustrative case is reported: surgical treatment corrected the carrier state and removed a dangerously infected kidney.

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FURTHER EXPERIENCE WITH ELECTRIC-SHOCK THERAPY IN MENTAL DISEASE*

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THE use of electric-shock therapy in the psychoses has become routine in many of the hospitals for mental diseases in the United States and in the private practice of many psychiatrists. An accumulated literature makes it possible to give with a greater degree of certainty the indications for the use of this method. These may be considered under two headings: injuries and risks, and accumulated experience regarding the type of case in which a favorable result may be anticipated and that in which little of value is to be expected.

Method of Treatment

Of the 123 patients in this series, 74 were treated by what I[1] have previously described as the "outpatient method" — that is, the patients reported at a place fitted out in hospital fashion with nurses and a physician in attendance, were given the shock treatment and, usually within one or two hours, went home. In a few cases, the patient was too disturbed after the treatment for the return home to be practical, and was transferred to a hospital for mental diseases to complete the series of treatments. In 2 other cases, injury precluded the return home, and transfer was made to inpatient care. In general, it can be stated that outpatient care of many psychiatric cases is very useful. It often makes commitment unnecessary, and although it must not in any sense be informal or without proper safeguard, it is, on the whole, as safe as inpatient care.

Injuries and Risks of Method

No fatalities have been recorded since the early days of the treatment. There is considerable difference of opinion concerning the pathologic cerebral changes produced. The Italian workers, Cerletti and Bini,[2] and Kalinowsky et al.[3, 4] found no serious neuropathologic changes in dogs. Smith and his co-workers[5, 6] found punctate hemorrhages in cats.

The fact that memory is definitely impaired for a variable period indicates that some organic change is produced. In the vast majority of cases, this impairment of memory disappears to a point where it is no longer discernible to the patient or to those around him. In other cases, there is some subjective difficulty in memory for several months, although not to the point of incapacity or disability. Since the best clinical results are often obtained when the patient is shocked into amentia, it may very well be that one of the conditions of recovery from a psychosis by the shock treatments depends on the temporary brain damage, probably most frequently swelling and possibly punctate hemorrhages. Only by speculation can one postulate a relevant change in any specific brain area or function.

Since the treatment has been in use in the United States for over three years and since cases have been observed for that period, it can now safely be stated that no severe damage of consequential type is done to the brain. Certainly, subdural and subarachnoid hemorrhages are not recorded in human beings. No neurologic signs have been noted after twenty-four hours in any of the cases that I have studied, and there is no record of such changes in the experience of other workers.

When the nature of the conditions treated and the suffering and doubtful prognosis are taken into account, it can on the whole be stated that the risk of brain damage by electric shock is fundamentally inconsequential when compared with the conditions treated: involutional melancholia, marked and severe depression, schizophrenia and the paranoid psychoses. Certainly, in an era in which hypothermia, hyperthermia, lobotomy and lobectomy are being carried out for the treatment of mental diseases, electric shock is, relatively speaking, a mild approach.

Injuries have been greatly reduced. The commonest complication is fracture of a vertebral transverse process. In this series of 123 cases, only 1 such fracture occurred. It was not disabling, and the patient recovered spontaneously and without orthopedic care. A fairly common type of injury in elderly people is either the precipitation of subdeltoid bursitis or its aggravation, if already present. Three such cases occurred in this series, and all responded to physiotherapy. The most unusual case of injury in the group was that of a fifty-year-old woman mentally sick for years with a chronic depressive state, presenting a moderate amount of osteoporosis common at her age and

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an anemia of considerable degree, who had a fracture of both acetabulums, with displacement of the heads of the femurs into the pelvis. Since this patient is still under treatment, the physical outcome cannot be stated. Mentally, she became clear after one electric shock and has remained so. It may be of value, consequently, to study the amount of calcium in the blood and to make a careful study of the bony structure of the pelvis in certain cases, although in the case mentioned above there was no basis for such a study from the history of the patient.

Electrocardiographic changes have been described as occurring within the first twenty-four hours after shock treatment. The recording returns to normal, however, within the same twenty-four hours. This may mean that the contraindications for treatment are severe arteriosclerosis, cardiac disease and very marked circulatory involvement. My own experience does not indicate any great degree of danger even with existing cardiac disease, although decompensation and severe arterial disturbances are certainly sufficient reasons not to undertake the treatment.

There are mental diseases, however, in which aggravated damage to the heart and circulation follows from the nature of the psychosis itself, as when an elderly patient suffering from cardiac and arterial disease becomes so intensely agitated and restless because of his profound emotional state that his circulation and the integrity of his heart become disturbed. Under such circumstances, I have weighed the risk of treatment against the risk of the disease and have given the treatment on the basis that the risk was warranted. There are 4 such cases in my records, of which I cite 2. One patient, a man with severe cardiac disease, frequent attacks of angina pectoris and one previous attack of coronary thrombosis, who presented the picture of a very severe agitated depression, recovered promptly after eight electric-shock treatments and has remained well; electrocardiographic studies made before and after treatment showed no change in the condition of his heart due to the electric shock. The other patient, a woman with myocarditis that warranted the use of digitalis in maintenance dosage, received seven shocks without any apparent damage to the heart or circulation, although her mental condition was only temporarily relieved. It can safely be stated that an ordinary degree of cardiac and vascular change need not be a contraindication if the psychosis warrants treatment.

Treatment was also given to a woman with a severe case of diabetes requiring 60 units of insulin a day. She received nine shock treatments over a considerable time, with no evidence of change in the diabetic state and with marked improvement in the mental state. There was a slight temporary change in the color of the urine after each treatment.

One patient with pernicious anemia, with a red-cell count of slightly over 2,000,000 and a hemoglobin somewhat under 50 per cent and with other evidence of vitamin deficiency, was treated (four shocks) with good results and without any effect on the pernicious anemia except perhaps in the direction of improvement, since her appetite returned and she ate a greater amount and a greater variety of food.

One case of Paget's disease in a man of over seventy was also treated (five shocks) by this method, without damage to the bony structure.

I believe that the technic used plays some part in the low rate of injury and that the physiology of electric-shock treatment is a significant factor in explaining the fact that moderate organic disease of the heart and other organs of the body is not a contraindication to the treatment. I have been very careful in the use of sandbags and a firm bed to support the back. Pillows have routinely been placed under the knees, so that it is impossible for the patient to get his feet down to the table and thus to put an extra strain on the back and other parts. Great care has been taken to prevent the shoulders from rotating outward and upward. A gag, made of felt and carefully inserted and watched during the procedure, has prevented any dislocations of the jaw; in fact, none have occurred for over a year.

The fact that with proper precautions few serious injuries take place is confirmed by most other reports. For example, the Boston State Hospital, which has given a large number of electric-shock treatments in the past year, has an exceptionally fine record so far as injuries are concerned. The method, therefore, may be declared safe. This, I repeat, does not mean that it is to be used indiscriminately, or without proper hospital conditions.

Unlike Metrazol, the electric-shock treatment causes a fall in the blood pressure. For a very short time, the patient is pulseless, but within a few seconds the pulse returns. There is less cyanosis than with Metrazol. There is no sweating. There is very little evidence of vasomotor disturbance. The gastrointestinal tract does not seem disturbed. There is rarely any nausea or vomiting, and there is no interference with the function of the bladder.

It has been recorded that there is a possibility of spontaneous epileptic attacks following shock treatment. The literature on this point is very scanty, and the evidence of such a result is not at

all conclusive. In fact, Kalinowsky et al.[3, 4] believe that electric shock offers a method of treatment for epilepsy. I have seen only 1 case in which there were epileptic attacks of minor type following treatment. This occurred in a fifty-nine-year-old woman with arteriosclerosis. After the treatment had been concluded, she had on successive days two short attacks of unconsciousness closely resembling those seen in arteriosclerosis, with some convulsive twitchings of the face and arms. There was no evidence of subdural or subarachnoid hemorrhage. In my opinion, the danger of setting up epilepsy by electric shock can be discounted.

Indications for Treatment

In considering the type of case that responds to this treatment, one must remember that psychiatric diagnosis has not reached the stage where it is possible to discriminate with any exactness between the various types of so-called "functional psychoses," such as schizophrenia, manic-depressive psychosis, involutional melancholia and the unclassified depressions, and the various severe neuroses. There is an abundant literature concerning this difficulty. Thus, a case diagnosed as schizophrenia by one clinician may be diagnosed by another as a marked depressive retreat. A patient who presents a neurosis at one stage of his mental disease may later show schizophrenia or some form of the depressive psychoses. Moreover, depressive psychoses may be substantially different, even though with the present inadequate methods of diagnosis and study they show a similar general clinical picture. Therefore, all statements regarding the value of this treatment can be regarded as only approximations to roughly delineated clinical syndromes, and disappointment in the result or even the unexpected good result cannot at present be explained.

In general, one may say that the electric-shock treatment is of little value in the fully developed schizophrenic state, with splitting of personality, hallucinations, delusions of reference, and negativistic or catatonic reactions — more especially, when the condition has lasted for years. Cases that are diagnosed as early schizophrenia sometimes do remarkably well, but the question of differential diagnosis is essential in an interpretation of the results. Thus, in one of my cases that had lasted for two years and had been diagnosed as schizophrenia, very good results were obtained with four shocks, and the recovery has lasted for six months. However, a study of the family history shows cases of manic-depressive psychosis, and the study of the past history of the patient herself is not at all conclusive of schizophrenia. It has been stated by some writers that schizophrenic patients need a large number of shocks for improvement or recovery. In 3 of this series of cases, more than fifty shocks were given, with no fundamental improvement in these well-marked schizophrenic states, the average number of shocks given in the other diagnostic groups being about seven, or even less. Conduct improvement often takes place, and temporary improvement is remarkably frequent. Unfortunately, in the vast majority of cases of clearly differentiated schizophrenia, the patient slips back into his previous state.

Electric shock is also of little advantage in the paranoid psychoses. Some cases with paranoid

TABLE 1. *Results of Electric-Shock Treatment of Mental Disorders.*

DIAGNOSIS	TOTAL NO. OF CASES	METHOD OF TREATMENT		RESULTS					
		HOSPITAL	OUTPATIENT	NO IMPROVEMENT	SLIGHT IMPROVEMENT	TEMPORARY IMPROVEMENT	MODERATE IMPROVEMENT	MARKED IMPROVEMENT	RECOVERY
Manic-depressive psychosis									
Manic phase	3	1	2	2	0	1	0	0	0
Depressive phase	20	9	11	1	0	2	7	6	4
Depression									
Recurrent depression	7	1	6	0	1	0	2	2	2
Depressive psychosis	6	4	2	0	0	0	2	1	3
Chronic depressive state	12	1	11	3	0	0	6	2	1
Agitated depression	3	2	1	1	0	0	0	1	1
Depressive state	7	3	4	0	0	0	3	0	4
Unclassified depression	2	0	2	0	0	0	2	0	0
Involutional melancholia	9	3	6	0	1	0	2	0	6
Senile melancholia	3	1	2	0	0	1	1	1	0
Anhedonia (unreality syndrome)	3	2	1	0	0	1	1	1	0
Schizophrenia	23	18	5	8	3	6	4	2	0
Paranoid state	4	2	2	4	0	0	0	0	0
Unclassified psychosis	2	1	1	0	0	1	0	0	1
Obsessive-compulsive state	6	1	5	2	0	2	2	0	0
Psychopathic personality	2	0	2	1	0	0	1	0	0
Psychoneurosis and anxiety state	11	0	11	5	0	2	4	0	0
Totals	123	49	74	27	5	16	37	16	22

coloring, that is, patients whose underlying state is fundamentally depressive, do very well. The patient believes himself to be persecuted, but when this delusion is analyzed, it is found that he is being persecuted because of his derelictions or for his good rather than because of the gratuitous hostility and malevolence of others.

In the obsessive-compulsive neuroses I have obtained no permanent benefit by the use of this method. The literature, on the whole, bears out this statement.

The involutional melancholias, with clearly marked depression, great agitation, anxiety, feelings of unreality or nihilistic delusions, on the whole do well with this form of treatment. This is the unanimous conclusion in the literature, and is borne out by my own experience (Table 1). One sometimes sees improvement in these cases after one, two or three treatments. The sequence of events seems to be that sleep is first restored, and that, as the memory becomes somewhat impaired, the delusions disappear and a genial and jovial mood replaces the melancholia. In a large number of cases, this improvement persists. There are relapses, however, and the treatment can by no means be called a cure. Nevertheless the improvement is so prompt and lasts in so many cases for so long that this can be called the best approach to the symptom complex at present.

Experience with senile melancholia in cases occurring after the age of seventy is insufficient for any conclusions. In 2 patients whom I have treated, there was marked temporary improvement, but no subsequent permanent gain.

The result of treatment of the depressive phase of the manic-depressive psychosis is similar to that of the individual melancholias. There is immediate improvement with treatment, usually after the third or fourth shock. The attack is frequently remarkably shortened in duration and intensity, and even where there is some slipping back, it does not generally reach the former level of despair and death seeking. It must be stated at this point, however, that when the attacks are frequent,—that is, when the cycle repeats itself every few months or even more frequently,—electric shock does not seem to me to be warranted. Part of the result of the treatment of the depressive states is the appearance of a mild euphoria. A manic state often supervenes, usually of less intensity than the depression, and often without any definite handicap to the patient. When the manic attack may appear at any time, however, it seems inadvisable to administer the electric shock. This statement is made because the manic attack itself does not seem in any fundamental way to be improved by shock therapy. Conduct improvement takes place, and a very wild patient is more easily managed. Within a week or two after the treatment has been terminated, the patient becomes as manic as ever. I have therefore discontinued the electric-shock treatment in the manic states, except when its use lessens the strain of the arduous care of the patient.

Very good results are obtained in cases of chronic depression, such as I[7] have elsewhere described as the "anhedonic state," and one cannot explain these cases on the basis of coincidence. In several such cases in my records, patients have remained anhedonic for several years and without improvement, despite the type of treatment used. Following a few shock treatments, the mood alters *pari passu* with the number of shocks given and the appearance of some impairment of memory. In some cases, a moderate exhilaration appears and persists for a long time, but is not troublesome.

Electric shock has not given marked relief in the neuroses, especially the anxiety neuroses that are marked by paresthesias occurring under excitement, with a sense of marked visceral disturbance, either of heart, head or other parts, and with marked fear localized as phobias or as diffuse agitation and anxiety. In these cases, the patient, usually being noncommittable, refuses to continue the treatment after a few shocks are given.

At this point, it is safe to say that the statement made in the literature that there is no fear of the treatment is not correct; there is less than with Metrazol shock, and often enough the individual treatment is not at all remembered. In the relatively sane patients, the whole matter of repairing to a hospital, of becoming unconscious and of a period of agitation and loss of memory afterward becomes linked up with the idea of treatment, and a definite association fear of the treatment develops. In the markedly psychotic cases, no such fear seems to be experienced.

I have not been able to treat in any consecutive manner such conditions as neurasthenia and hysteria. In a few chronic cases, I have attempted to carry out the treatment, but the patients have themselves put an end to this by refusing to undergo more than one, two or three shocks.

Summarizing the indications, one may say that when a disturbance in affect or mood is the main psychopathologic feature, electric-shock treatment has a very reasonable prospect of bringing about marked improvement, recovery or, at the worst, remission. This includes the depressive states, the anhedonic states and the cases of involutional melancholia. This is not true, however, of the affective disturbance called the manic phase of manic-depressive psychosis. In functional or nonestab-

lished pathologic mental diseases, such as schizophrenia, the paranoid psychoses, the obsessive-compulsive states and the anxiety neuroses, the results have not been particularly gratifying. Temporary improvement is common; permanent or durable improvement is not frequent. When the differential diagnosis is in doubt, — that is, when it is difficult to differentiate a mental disturbance of the schizophrenic type and one belonging on the whole to the mood-and-affect disorders, — it is justifiable to use this method, since on the whole no harm is done and the prognosis is so poor as to warrant anything that offers hope.

In Table 1, the diagnoses include a great variety of depressions that some other workers might perhaps classify with the manic-depressive states. The difference is that certain classic phases of the manic-depressive state did not occur in this group of patients. Most of them were not retarded, a good many had no delusions of any kind, and some were definitely not psychotic in the technical sense. The main feature in common was an affect disturbance of a depressive nature.

It is necessary to define the term "anhedonia-unreality syndrome." By this is meant a state in which there is complete lack of desire and satisfaction for the visceral enjoyments, such as eating, sleeping and sexual relations, as well as a failure in energy and the capacity to work, linked with a feeling of unreality sometimes related to the outer world and sometimes including the patient himself. It is possible that this group of cases is also allied to the manic-depressive state. The patients are not insane in the usual sense and have good insight.

By the term "slight improvement" is meant conduct alteration and a lesser expression of the psychosis. "Temporary improvement" goes farther: the patient seems quite well for a short time — two or three weeks to two or three months. "Moderate improvement" means that the patient shows conduct improvement and a general lessening of psychotic and mental symptoms directly following the treatment and maintained indefinitely. By "much improvement" is meant an extension of this classification further, difficult to make quantitatively but representing a clinical impression. "Recovery" means that the particular attack disappears and, so far as can be seen, there are no mental signs whatever.

Summary

The injuries resulting from electric-shock therapy, and the risks encountered, are discussed. The indications and contraindications in various neuroses and psychoses are considered. Experience with this form of therapy in 123 cases of mental disorders is presented.

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CLINICAL NOTES

ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS ASSOCIATED WITH FINGER LESIONS RESEMBLING LUPUS PERNIO*

Report of a Case

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THE following case is of interest because the initial lesions were seen on the tips of the fingers, when a diagnosis of lupus pernio was made. However, the typical butterfly lesion of the face soon appeared, and the patient complained of abdominal pain, nausea and vomiting, and muscular and joint pains; these symptoms clinched the diagnosis of lupus erythematosus disseminatus.

Case Report

G. C., a 15-year-old girl, was first seen at the Medical Clinic of the Out-Patient Department, Boston City Hospital, in December, 1938, complaining of loss of energy, general malaise and stiffness and soreness of the fingers of both hands for the previous few weeks. The patient was referred to the Skin Clinic in January, 1939. Physical examination revealed erythematous infiltrations on the flexor and lateral aspects of the fingers. These areas were rather tender. The hands were cold and clammy. A diagnosis of lupus pernio was made.

During the next week, ulcerative changes were observed on the skin of the fingers. The volar surface showed several round to oval lesions 2 or 3 mm. in diameter, with smooth raised red edges and central scaling depressions. Physical examination was negative except for the fingers. Two weeks later, a faint butterfly lesion on the face was evident. X-ray examination of the hands, feet and lungs was negative. Tuberculin tests in dilutions of 1:10,000 and 1:1000 were negative. The blood Hinton reaction was positive. Biopsy showed hyperkeratosis and no atrophy of the epidermis, acanthosis, and elongation and matting of the rete pegs. The corium showed lymphocytic and perivascular infiltrations; there was no evidence of true tubercles. At this time, weekly injections of 1 cc. of bismuth were begun. After eight such treatments, there was a marked improvement, the central depressions of the lesions of the fingers becoming less evident and the erythematous color fading to normal skin color. A blood Hinton reaction was doubtful, but both Kahn and Wassermann reactions were negative.

The patient was admitted to the hospital in June. Three days before admission, she had noted fever, without chills. In the mornings, there was mild nausea, and vomiting occurred soon after eating. There was mild, cramplike abdominal pain.

Physical examination revealed an erythematous patch, 3 cm. in diameter, above the bridge of the nose, herpetic lesions about the nose and mouth, and hemorrhagic oval lesions, 5 mm. in diameter, on the hard palate. The lungs were clear, and examination of the heart revealed no murmurs. The abdomen showed generalized and rebound tenderness. The liver and spleen were palpable at the costal margins. The volar surface of the fingers showed reddish-purple, oval, depressed atrophic patches, 5 to 10 mm. in diameter. The hospital stay was characterized by an elevated temperature (103°F.), which gradually fell to normal in 2 weeks. The daily urines showed albumin except for two specimens. The white-cell count, which was 2300 on admission, gradually rose to normal by the 7th hospital day. The patient became asymptomatic at the end of the 2nd week, and was discharged on the 23rd day with a diagnosis of lupus erythematosus disseminatus.

The patient returned to the Skin Clinic and was again given 1 cc. of bismuth weekly. In November, 1939, she was seen at the Vascular Clinic, and a diagnosis of Raynaud's disease was made. In May, 1940, she was exposed to the sun and developed the typical butterfly patch of lupus erythematosus on the face. Two weeks later, she began to have soreness of the throat and morning bleeding from the mouth, gums and throat, accompanied by a weak and feverish feeling. Hospitalization was advised.

The patient was readmitted to the hospital in June. The face showed a red, slightly raised eruption confluent except at the periphery, where there were isolated papules, not indurated, blanching on pressure, with prominent follicles on the involved area, and a roughly butterfly distribution involving the nose and cheeks and extending up to the ears and the sides of the face and over both eyebrows. There were slightly indurated papules becoming confluent over the upper lip, involving both the skin and the mucous membrane. Multiple small circinate red lesions 1 to 3 mm. in diameter were seen over the gums, hard palate and gum margins. The thorax and abdomen showed lesions like those on the fingers. The tongue was coated and fissured. The teeth were carious. The tonsils were moderately enlarged but showed no redness; the hair showed evidence of alopecia. The pupils were slightly irregular but reacted to light and distance, and in the right fundus, a fading flame-shaped hemorrhage was observed; pea-sized axillary and inguinal nodes and bean-sized tonsillar nodes were palpated; the trachea was in the midline. The lungs were clear to percussion and auscultation. The heart was enlarged, rapid, regular and overactive, and the pulmonic second sound was greater than the aortic; there were blowing systolic murmurs at the apex and in the pulmonic area. The abdomen was flat, with no spasm or tenderness. The liver was felt 3 cm. below the costal margin; the edges were sharp and soft. The spleen was 1 cm. below the costal margin in the left lateral position. The reflexes were physiologic. The blood pressure was 104/64.

Daily examinations of the urine showed a specific gravity of 1.010 to 1.020, an acid reaction, and slight traces to traces of albumin in all but three specimens. The sediment contained a few to many white blood cells, usually in clumps, very rare red blood cells on only one occasion and coarse granular casts just before death.

The hemoglobin, which was 75 per cent on admission, fell to 45 per cent 3 days before death. The red-cell count was 3,800,000 on admission and 2,700,000 before death. The white-cell count varied between 5200 and 5000; differential counts on admission showed 78 per cent polymorpho-

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nuclears, 17 per cent lymphocytes, 1 per cent monocytes and 5 per cent young forms. The blood Hinton reaction was positive on three occasions and doubtful twice. The blood Wassermann and Kahn reactions were negative on two occasions. The nonprotein nitrogen was 41 mg. per 100 cc. on admission, rising to 60 mg. 4 days before death. The total protein, which was 6.6 gm. per 100 cc. on admission, was 6.5 gm. 10 days later. The albumin-globulin ratio was 3.9:2.6. The blood sodium was 133 mg. per 100 cc.; 2 weeks later, it was 130 mg. The chlorides were 571 mg. per 100 cc. The potassium was not recorded. The calcium was 8.5 and the phosphorus 5.1 mg. per 100 cc. The phosphatase was 3.2 Bodansky units. Four blood cultures revealed no growth, but one culture showed streptococcus; subsequent cultures were negative. The phenolsulfonephthalein was 44 per cent in 2 minutes. The Widal test was negative. The clotting time was 15 and the bleeding time 3 minutes. The mean corpuscular volume was 93 per cent. The prothrombin time was 31, and the coagulation time 13 minutes. The icteric index was 7, the urobilinogen 1.8 mg. per 100 cc., and the sedimentation rate 1.7. Three stool examinations revealed negative guaiac reactions.

A chest plate revealed clear lung fields.

An electrocardiogram showed normal sinus rhythm, a PR interval of 0.16 second and a QS complex of 0.06 second; T_1 was upright, T_2 was flat, and T_3 and T_4 were inverted. The left ventricular predominance was interpreted as showing myocardial disease.

The patient was hospitalized for 26 days, during which she steadily failed. The temperature varied from 100 to 102°F. daily. There was mild generalized abdominal pain, with nausea and intractable vomiting. The lesion on the face faded somewhat, but the mucous-membrane lesion progressed and became confluent. Frequent nosebleeds and hemorrhages from the gums were present. At the end of the 3rd week, the patient was having severe gastrointestinal symptoms, vomiting and abdominal pain, hyperpyrexia (104°F.) and increasing asthenia; she had lost 10 pounds since admission. The blood pressure rose somewhat with administration of 10 mg. desoxycorticosterone daily. On the 26th hospital day, the patient went into peripheral vascular collapse, and death followed in a few minutes. No autopsy was performed.

This case of acute disseminated lupus erythematosus is reported because of the unusual sequence of symptoms and physical signs shown by the patient, and because the opportunity to follow a patient from what is deemed clinically a benign symptom complex to a later fatal disease is rare. The uncommon but confusing laboratory findings, in view of state laws demanding serologic examinations before marriage, should be of interest to all physicians. This case shows that the dermatologic eruption was only a physical sign of a serious systemic disease that was further complicated by abdominal symptoms suggesting the need of surgical interference.

520 Commonwealth Avenue

THE USE OF IODINE TO DELINEATE A SAFETY ZONE IN THE RECTUM*

DAVID C. DITMORE, M.D.†

BOSTON

WHEN or by whom iodine was first used as a vital tissue stain, I do not know. However, the fact that certain cells take up the dye more readily than others was first brought to the attention of the medical profession by Schiller‡ in his work on the early diagnosis of cancer of the cervix. I have found that the affinity of the tissues just above the pectinate line of the rectum for the simple tincture or the compound solution of iodine varies so decidedly that the use of either is of great assistance when one is working in this area. In fact, there is definitely outlined the distal border of a portion of the rectal wall that, since it has little tendency to bleed and does not respond to painful stimuli, may be termed the "safety zone." The existence of this zone is so manifest and the test to locate it so simple that I hesitate to claim anything new in it, but general knowledge concerning the phenomenon is lacking, I am quite sure, and for that reason I shall describe the technic of its demonstration.

After a swab of cotton on an applicator is dipped into the iodine, it is withdrawn and held momentarily against the mouth of the container so that any excess fluid may escape. The area to be investigated, already isolated in the anoscope, is then prodded gently with the iodine-soaked swab. If no change in color appears, the anoscope is slowly withdrawn with the free hand, while prodding with the iodine swab is continued. At some point above the pectinate line, the tissue will be seen to become deep black.

The stained area follows no uniform pattern. In some cases, there may be a continuous or broken band no more than 2 or 3 mm. in width tracing the upper border of the pectinate line. On the other hand, the stained area may be from 15 to 20 mm. in width, with the upper border very irregular. Regardless of the extent of the heavily stained tissue, the operator may, by confining himself to the zone immediately proximal to it, proceed with minor surgery without fear of complications such as excessive bleeding, pain and external edema. He must, of course, observe ordinary surgical technic.

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‡Schiller, W. Zur klinischen Frühdiagnose des Portiokarzinoms. *Zentralbl. f. Gynäk.* 52:1886-1892, 1928.

I am not qualified to discuss the mechanism of this staining reaction. Much has been written about it. Everyone seems to agree that columnar cells do not take the stain, whereas cuboidal or squamous cells with a high content of glycogen stain readily. I have never seen it mentioned that highly vascular tissue stains more readily than avascular tissue, but this seems to be true, at least in the lower rectum.

The practical values of this test are many. For example, in the safety zone, biopsy, insertion of a hypodermic needle and removal of small benign tumors are simple procedures. Proximal or distal to that area, the same operation may cause much unhappiness both to the physician and his patient.

Conclusions

Variations in the affinity for iodine of the normal tissue cells of the anorectum are as striking as those described by Schiller in his work on carcinoma of the cervix.

Taking advantage of this property, one can roughly locate the pectinate line and establish a safety zone in which minor surgical procedures may be carried out.

7 Bay State Road

MEDICAL PROGRESS

RADIATION THERAPY

Richard Dresser, M.D.*

BOSTON

THE recent advances that have been made by physicists and engineers in the construction of x-ray generators have placed at the disposal of the radiotherapist a wide variety of wave lengths in intensities greater than were dreamed of a decade ago. It is natural that some confusion regarding the relative merits of these wave lengths should exist, not only in the minds of practitioners but also among radiologists themselves. Although the clinical results of radiation treatment can be evaluated only after years of painstaking observation, the intelligent application of roentgen rays or radium rays should be based on a knowledge of their physical properties as well as their biologic effects. The physics of radiology has been set forth simply and concisely in a recent treatise by Robertson.[1] A review of this work should help the practitioner to understand some of the problems that confront the specialist in radiation therapy.

Radium is an element that is continually disintegrating. In the process of decay, three types of energy are given off—alpha, beta and gamma rays. If the rays from a radium source are submitted to the action of a strong magnet, the alpha rays are deflected in one direction and the beta rays in the opposite direction; the gamma rays are unaffected by the magnetic field. The alpha rays are actual particles of matter bearing a positive electric charge. The beta rays, which are likewise particles of matter, carry a negative charge. The gamma rays have no mass, but are ethereal vibrations. The alpha rays may be disregarded in therapeutic work, since they have little penetrating power and are filtered out by the walls of the radium container. The beta rays have some penetrating power and are frequently used, particularly in the field of dermatology, for the treatment of superficial lesions. The gamma rays are the most important of the radium rays. They have essentially the same properties as x-rays but are much shorter and more penetrating than the x-rays in common use. Recently, it has been possible to produce x-rays that are as short or even shorter than the gamma rays of radium.

Radium element is most commonly used in the form of one of its salts, either the sulfate or bromide. Metal tubes are filled with the salt and sealed off at either end. Frequently, the tube has an eye at one end and a point at the other, forming what is known as a radium needle. This type of applicator may be inserted into a tumor mass and withdrawn, after the required dose has been given, by means of a string threaded through the eye. It is often desirable in radium treatment to exclude the beta rays, leaving only the penetrating gamma radiation. This is done by interposition of a metal screen or filter between the radium source and the tissue irradiated. It is now common practice to make the wall of the container itself of some metal of sufficient density and thickness to remove all beta radiation without additional screening. The commonest filters, listed in order

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of their effectiveness, are platinum, gold, lead, silver and brass. Radium dosage, when the element is used, is expressed in milligram hours: that is, the number of milligrams employed multiplied by the time of application in hours. Thus, 10 mg. applied for five hours would give a dose of 50 mg. hr. Likewise, 25 mg. applied for two hours would give the same dose.

Another form in which radium is used is known as radium emanation or radon. Radon is a gas that is given off from radium and, by means of a specially designed pumping and purifying system, can be collected in capillary tubes of glass or gold. The development of the so-called "radium emanation plant" was due in a large measure to the researches of the late William Duane, professor of biophysics at Harvard University. After the capillary tubes have been filled with radon, they are cut into small sections, which are automatically sealed in the process of cutting. These capillary sections are known as radon seeds or implants. They emit both beta and gamma radiation; however, if a gold capillary is used, a large percentage of the beta radiation is filtered out. The great difference between radium element and radon is that the former takes one thousand six hundred and ninety years to degenerate to half strength, whereas the latter becomes inactive for practical purposes in about thirty days. One makes the application of radon seeds by placing the implant in a suitable trocar. The trocar is pushed into the neoplasm to the desired depth, and a stylet then pushes out the seed. When the trocar is withdrawn, the seed remains in the tumor. Radon dosage is expressed in millicurie hours, 1 mc. hr. being equal in intensity to 1 mg. hr. Each millicurie of radon delivers, in its decay period of thirty days, 130 mc. hr. Thus, if a seed of 2-mc. strength is inserted, the total dose is figured as 260 mc. hr. Radon seeds may be employed to advantage in locations where it would be difficult to insert or to hold element needles in place,—for example, in a carcinoma of the tonsil.

Credit for the development of an x-ray tube whose output can be accurately controlled is due Coolidge, former director of the research laboratories of the General Electric Company. When a wire is heated to incandescence in a vacuum tube, small negative particles of electricity are liberated about the wire. This is known as ionization by heat, or the Edison effect. By application of a high-voltage current to the tube, these ions may be drawn away from the wire filament and made to move at high velocity toward the target or anode of the tube. The impact of the electrons against the anode, which is usually a block of tungsten, results in x-ray production. It has already been noted that the commonly employed roentgen rays are identical with the gamma rays of radium except in wave length.

The physical properties of x-rays may be considered from the standpoint of intensity or quantity, and of quality. If the amount of current applied to the tube is varied, the amount of x-ray emitted varies in direct proportion. If, however, the voltage of the current is varied, the x-ray output varies approximately as the square. More simply, if the voltage on the tube is increased from 100,000 to 200,000, all other factors remaining constant, the x-ray production will be quadrupled. X-rays and light rays follow the same law in regard to distance: that is, the intensity varies inversely as the square of the distance. For example, if one assumes that it takes ten minutes to administer a certain x-ray dose at a distance of 25 cm. from the source of radiation to the skin of the patient, and if this distance is doubled,—that is, increased to 50 cm.,—not one half but one fourth the amount of radiation reaches the patient. It then takes not ten but forty minutes to give the same x-ray dose.

To explain variations in the quality of radiation, one may draw an analogy between a beam of x-rays and a beam of sunlight. When sunlight is passed through a glass prism, the well-known spectrum results, because of a breaking up of the beam into its constituent wave lengths. The violet band at one end of the spectrum represents the shortest visible wave lengths, whereas the red band at the opposite end represents the longest visible wave lengths. By passing an x-ray beam through a prism, let us say of rock salt, one can obtain an analogous spectrum. This, of course, is not visible, but the various bands can be recorded by photographic and other methods. It will be found that the beam is not homogeneous but is composed of a variety of wave lengths. By raising of the voltage on the x-ray tube, shorter wave lengths are added to the beam; there is more "violet" radiation if one uses the analogy of the light spectrum. If the potential is increased to between 2,000,000 and 3,000,000 volts, the short wave lengths of the beam are identical with the shortest gamma rays of radium. If one wishes to employ only the short wave lengths of an x-ray beam, the longer rays must in some manner be excluded. This is done by the use of filters, as in radium work. The common filters are lead, copper, a combination of tin and copper, and aluminum. Lead is used in filtering rays produced at 1,000,000 volts and upward. Copper, or tin and copper are used for rays of 200,000 to 500,000 volts, and aluminum for rays produced at 100,000 to 150,000 volts.

X-ray dosage is commonly expressed either in

terms of the visible effects on the skin or by a physical measurement of intensity known as the roentgen unit (r). If a certain amount of radiation is given to the skin, a mild redness appears in ten days to three weeks after exposure. The amount of radiation necessary to produce this effect is called the "erythema dose." A slightly smaller amount causes epilation of a hairy area, and is known as the "epilation dose." X-rays passing through the air cause an electrical upset in the atoms that is termed "ionization." The amount of ionization is directly proportional to the intensity of the x-ray beam. The roentgen unit is based on a physical measurement of the amount of ionization occurring in 1 cc. of air. It has become the internationally accepted standard of x-ray dosage.

The treatment of superficial lesions concerns chiefly x-rays of long wave length — that is, the relatively nonpenetrating variety. Many benign dermatologic conditions, together with cancerous or precancerous lesions of the skin, can be adequately handled by rays produced at not more than 100,000 volts. Any good radiographic machine equipped with the proper tube is entirely adequate to handle such cases. If, however, a lesion is situated at some distance below the surface, it is obviously impractical to attempt treatment with 100,000-volt x-rays whose energy is largely dissipated within the first 2 or 3 cm. of tissue. One must resort to shorter wave lengths, which necessitate high voltage for their generation. A second factor of equal significance in the treatment of deep-seated lesions concerns the inverse square law. For example, a carcinoma of the body of the uterus is to be irradiated; this organ is located approximately at the center of the pelvis, about 10 cm. from the surface in the average patient. If the source of radiation were placed 10 cm. from the patient's skin and the absorption of energy in the intervening tissue entirely disregarded, only 25 per cent of the dose delivered to the surface would reach the tumor. If the source were moved to 50 cm. from the patient, it would take twenty-five times as long to give the dose to the skin, but the tumor would receive 69 per cent of the surface radiation. This is a purely theoretical consideration, and in actual practice, the figure of 69 per cent would be considerably reduced by tissue absorption. Radium would afford an ideal source of energy for external application if it could be obtained in sufficient quantity. However, when the amount of radium ordinarily available is placed at sufficient distance from the patient to deliver an adequate depth dose, the time of application becomes so long that the method is not practical. The commonly employed "deep therapy" x-ray unit, which operates at about 200,000 volts, can be used at distances of 50 to 80 cm. without undue prolongation of the treatment time. The amount of radiation delivered below the surface with this type of therapeutic apparatus is greater than that obtainable from the usual radium application. Radium is chiefly valuable in the treatment of readily accessible, fairly well-localized growths, in which it can be used by direct application or by implantation. Frequently, a combination of x-ray and radium therapy is advisable, one treatment supplementing the other.[2]

Roentgen rays generated at potentials considerably in excess of 200,000 volts are now available, and are known as "supervoltage rays." It has been possible to produce these rays in tremendous intensities with wave lengths as short and penetrating as the gamma rays of radium. The treatment time at a distance of 100 cm. or more is relatively short. It should be emphasized that there is nothing new in the quality of supervoltage x-rays. The advocate of radium therapy becomes, unwittingly or otherwise, an advocate of supervoltage roentgen therapy, since the two types of radiation can now be made identical.

As the wave length of an x-ray beam is decreased, — that is, as the voltage and filtration are increased, — certain physical and biologic changes have been observed: there is an increase in the amount of radiation delivered below the surface (depth dose); there is a lessening of skin reaction (it takes more roentgen units to produce an erythema); the size of the portal of entry has less effect on depth dose; and there is less scattered radiation. These facts have been established beyond question.[3–5] A review of the conflicting observations on the therapeutic value of supervoltage x-ray would, at present, be confusing. However, an intense source of radiant energy of a quality equivalent to the gamma rays of radium is certain to occupy a major place in the armamentarium of the radiotherapist.

The method of application of radium or roentgen rays varies in some degree with the training and experience of the radiologist. A small, accessible growth may often be successfully treated by a single intensive dose. The radiation necrosis resulting from such therapy will heal satifactorily, provided the area irradiated is not too large. If the disease is extensive or deeply situated, the so-called "divided dose" is usually employed. This consists of relatively small amounts of radiation administered daily, or perhaps at longer intervals, with an extension of the treatment series over a period of days, weeks or even months.[6] Presumably, neoplastic cells have a slower rate of recovery from the damaging effects of radiation than nor-

mal cells, and it is on this basis that the divided-dose technic has been established. The aim is to build up a total intensity that will be lethal to cancer tissue, but from which the normal structures included in the field of radiation will recover.

A reasonably acurate prognosis following radiation therapy is not only difficult but frequently impossible. The pathologist can be of considerable help, but one must still rely to a large degree on the method of trial and error. Warren[7] states:

> While it may be said that, as a rule, less differentiated tumors are more radiosensitive, this is not completely correct. Indeed, our knowledge of the response of various tumors to irradiation rests largely on empirical grounds. It should be mentioned in passing that while histologic grading of malignancy is of some assistance in estimating radiosensitivity, many tumors of the higher grades are radioresistant, and some of the lower grades radiosensitive. Even with tumors of the same histologic type there may be variation in response, and even in the most resistant types an exceptional case may respond well to radiation therapy.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 28371

PRESENTATION OF CASE

First admission. A fifty-nine-year-old Portuguese unemployed cabinet-maker was admitted to the hospital because of hematuria, followed by pain in the back and a chill.

The patient was in good health until ten days before entry, when he began to pass bright-red blood in the urine. The urine then became a persistent, uniform dark brown. Dull backache developed, about equally on both sides. The pain was unrelated to respiration and was not relieved by strapping. The day before entry, the patient had a shaking chill followed by profuse perspiration. There was no nocturia, dysuria or other urinary symptom.

Thirty years before admission, the patient had gonorrhea, characterized by an acute urethral discharge. This was cured after several months' treatment. A few years later, some bright-red blood appeared in the urine without antecedent manipulations, and the urine became dark colored. The patient took some pills, and the urine again became normal. At no time were there any symptoms of stricture. No instruments were ever passed. Nine years before entry, the patient began to have burning epigastric distress coming on just before meals and usually relieved by food. Acid and gaseous eructations were associated. An "ulcer" was demonstrated by roentgenogram, and medical treatment was instituted. After two years, the symptoms previously noted became severer, with stabbing pain, vomiting and tarry stools. Roentgenograms taken in this clinic and in another metropolitan hospital showed an active duodenal ulcer. Ultimately, subtotal gastric resection, with posterior Polya anastomosis, was performed in this hospital. The postoperative course was uneventful, and the patient remained symptom free in the four years preceding his re-entry for different complaints.

On admission, the patient appeared frail, thin and ill. The heart was of normal size, with distant sounds. The lungs were normal. There was well-defined tenderness in the left costovertebral angle, without spasm or palpable mass. The abdomen was normal except for the scar of the previous laparotomy. The prostate was one and a half times normal size and rubbery, without nodules.

The blood pressure was 130 systolic, 80 diastolic. The temperature was 100°F., the pulse 80, and the respirations 18.

Examination of the blood showed a red-cell count of 4,400,000 with 70 per cent hemoglobin, and a white-cell count of 9600 with 69 per cent polymorphonuclears, 22 per cent small lymphocytes, 7 per cent monocytes and 2 per cent eosinophils. The blood Hinton reaction was negative. The nonprotein nitrogen was 33 mg. per 100 cc. The urine showed a ++ test for albumin, with many red and white cells in the sediment.

An intravenous pyelogram showed prompt excretion of the dye. The upper calyxes of the left kidney were slightly dilated, but the corresponding pelvis was not visualized. The right renal pelvis and calyxes were normal. The kidney outlines were not visible. The spine showed lateral curvature and rarefaction of the bones, without evidence of metastatic lesions. There was a large filling defect in the base of the bladder suggesting an enlarged prostate, and the bladder showed trabeculation.

A second intravenous pyelogram failed to confirm a filling defect in the left pelvis. A flat roentgenogram of the abdomen showed normal kidney shadows.

Following dilatation of a stricture of the urethra, cystoscopy was performed. The bladder was markedly trabeculated, but no stones or tumor was evident. The median lobe of the prostate was hypertrophied. Urine cultures taken from each ureter grew colon bacilli, and were negative for tuberculosis on guinea-pig injection.

A left retrograde pyelogram showed definite dilatation of the upper calyxes, but was otherwise unsatisfactory owing to movement of the patient. On the sixteenth hospital day, the patient was discharged, pending the report on the urine cultures.

Second admission (three weeks later). Four days after discharge from the hospital, the patient noticed recurrence of slight ache in the back and flanks. Four days later, severe pain appeared in both left and right flanks, associated with chills and two episodes of gross hematuria. The flank pain became increasingly severe. There was constant malaise.

On re-examination, the patient appeared essentially as before. Costovertebral tenderness was marked on the left and but slight on the right.

The temperature was 102°F., the pulse 90, and the respirations 25.

Laboratory data were much as before. The white-cell count was 28,400.

The day after entry, ureteral catheterization was attempted, but resistance was encountered high in the left ureter. The next day, the patient was less sensitive over the costovertebral angles, but complained of pain over the mastoid process. There were no physical signs of parotitis. The patient was given sulfathiazole, with a prompt fall in the temperature. An intravenous pyelogram showed no essential changes from earlier examinations. Roentgenograms of the cervical and dorsal spine were essentially negative. After a week and a half, the patient still complained of pain in the neck. Retrograde pyelography of the left kidney was again unsuccessful, owing to ureteral block. A rise in temperature followed the manipulation.

Roentgenograms of the gastrointestinal tract showed a large pocket of air and fluid beneath the dome of the left diaphragm, posteriorly, measuring 7 cm. in diameter (Fig. 1). The lower and medial borders of this cavity were irregularly lobulated. No barium could be brought into the cavity from the gastrointestinal tract. The remnant of the stomach was displaced to the right and anteriorly. The splenic flexure of the colon was displaced downward. Smaller, irregular, air-filled spaces lay in the left midabdomen below the large cavity. The midportion of the small intestine was displaced forward slightly, on the left. On the thirty-second hospital day, an operation was performed.

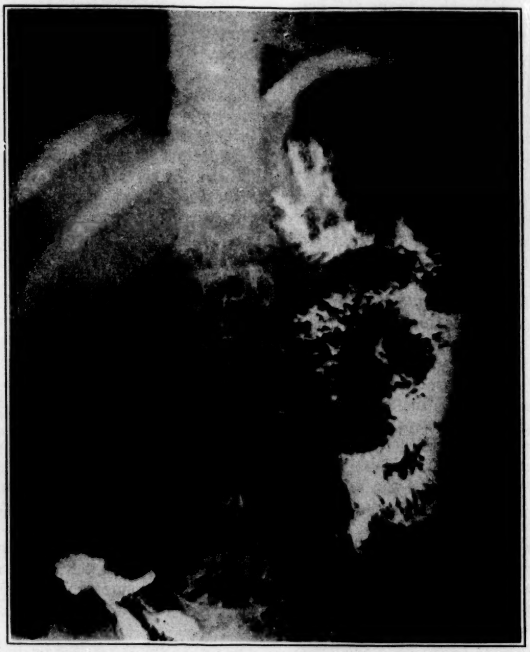

FIGURE 1. *Roentgenogram Showing Large Pocket of Air and Fluid beneath the Dome of the Left Diaphragm.*

DIFFERENTIAL DIAGNOSIS

DR. WILLIAM C. QUINBY*: "The urine then became a persistent, uniform dark brown." This has no specific significance except that it means that the blood was shed some time before it appeared. One does not as a rule find a patient passing urine of this type unless there has been precipitation of hemoglobin. The change to brown color has very little clinical significance.

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"Subtotal gastric resection, with posterior Polya anastomosis, was performed in this hospital." That is an operation, as I understand it, in which one reduces the size of the nonacid-producing part of the stomach by a resection of its terminal portion. Nothing is said about the specimen removed at that operation.

I do not know what the term "rubbery" means. It could be anything from sponge rubber to bakelite, I suppose. There were no nodules, and no suggestion that the prostate was carcinomatous.

The hemoglobin and red-cell count were not low for a person said to appear chronically ill. Evidently, the hematuria was no longer severe. The white-cell count was also not suggestive of any severe infection. The renal function seemed normal.

On intravenous pyelography, there was seen some suggestion of dilatation of the upper calyxes on the left — the side on which tenderness had been elicited. The pyelogram on the right was normal. "The kidney outlines were not visible." One is interested to know why they were not, but no explanation is given. In a patient who is thin and chronically ill, it should be possible to see the outline of the kidney in a properly exposed film, unless a soft-tissue mass or gas or something of that sort obscures the renal shadow. At a second pyelography, however, the renal shadows appeared normal. At this time also, the "pyelogram failed to confirm a filling defect in the left pelvis." Does this mean that the pelvis appeared normal, or just what does it mean? We are not told.

A cystoscopy was performed; presumably, whatever stricture may have been present was easily dilated, so that the instrument could be passed, and therefore had played no part in the patient's difficulties. Nothing much is said about the prostate on this examination except that there was "hypertrophy of the median lobe." Since the prostate was found to be enlarged on rectal palpation, there must have been some other enlargement than that of the median lobe, for this cannot be felt rectally. No statement regarding residual urine appears. On the whole, I must exclude the prostate as the cause of the patient's illness. A left retrograde pyelogram showed dilatation of the upper calyxes. Here, again, we have some confirmation of the first intravenous pyelogram. Cultures of the urine showed the colon bacillus present in each kidney.

During the three weeks out of the hospital, the patient did badly, and had more bleeding and back pain; although this was in each flank, palpation revealed much more tenderness on the left. At this time, his poorer condition is evidenced by a leukocytosis and fever. At a second cystoscopy, the statement is made that resistance to the passage of the catheter was met "high in the left ureter." But this is again indefinite. Did the catheter pass 20 or 25 cm., the normal distance being 30 cm.? We do not know. Also, neither at this nor at the previous cystoscopy was there any mention of bloody urine from either catheter. We do not know whether to assume that the hematuria was from the left or the right side, or neither.

Pain over the mastoid process is a queer complaint in this story. I should like to know whether there was any evidence of infection, such as discharge from the ear. Nothing is said about it. They did not x-ray the mastoid process, but they did x-ray the cervical spine, with negative results.

Two further x-ray examinations were made in an endeavor to learn more about the left kidney. The intravenous injection showed nothing more than before, and the retrograde route again found a blocked ureter. Ten days later he "still complained of pain in the neck." I do not know what this means. At this time, however, x-ray study of the gastrointestinal tract "showed a large pocket of air and fluid beneath the dome of the left diaphragm." This, of course, is a very important and evidently new finding. May we see the x-ray films?

DR. LAURENCE L. ROBBINS: The first thought on seeing this cavity was naturally that it was an unusually large gas bubble in the fundus of the stomach. However, two smaller gas pockets were present below the large one. As soon as barium was given, it became evident that the gas was external to the gastrointestinal tract. We naturally suspected a connection with the stomach but were never able to force any barium into the cavity.

DR. QUINBY: What relation did it have to the colon?

DR. ROBBINS: So far as we could make out from the films, — there were other films that showed barium in the bowel twenty-four hours after the gastrointestinal examination, — the colon was displaced downward. The air appeared to lie under the diaphragm.

DR. QUINBY: What can we say? What kind of diagnosis is it possible to make to tie all these things together? There was air under the diaphragm. A perforated viscus (of which we have no evidence) may be the cause, or perforation of an abscess containing the colon bacillus. I do not believe we need to postulate a communication with the bowel because we find a collection of air in the peritoneal cavity. One usually does find a communication, such as a perforated peptic ulcer,

but I think in this case it is safest to go on the evidence of the roentgenologist and at least assume that the cause of the air was not primarily bowel.

We must consider the question of the operation, a resection of the stomach four years previously. In the meantime, the patient was perfectly well. That type of resection is not made as a rule for cancer, which in a duodenal ulcer is not nearly so common, although it does occur, as in an ulcer situated on the proximal side of the pylorus — namely, a gastric ulcer. But each of these areas had been removed. It is accordingly very difficult to see how this manifest abscess had anything to do with the previous operation, or how it had any special connection with the intestine. Also, it was on the left side, bearing no relation to a septic pylephlebitis or liver abscess.

I thought first of actinomycosis (not very uncommon in the intestine) involving the colon and kidney, of which there is no evidence. There is no justification for assuming that the prostate contained neoplasm. Could this phenomenon follow a neoplasm primary in the kidney? Probably not. I have seen cases in which a tumor of the kidney, a hypernephroma, became necrotic and secondarily infected, and such patients may show no evidence of infection in the urine, but have general systemic evidence of infection and sometimes even a positive blood culture. The colon bacillus might of course form gas in the necrotic area of such a rapidly growing neoplasm. This seems rather farfetched here, for we have no evidence of renal tumor in any of the examinations or pyelograms produced. Here is the film of which the report was that the upper calyxes were somewhat dilated, but nothing more was seen. Here is the intravenous injection and here the retrograde injection, and in neither is there anything significant.

We come then, so far as I can see, to infection in some way related to the kidney that had formed an abscess, which, in turn, had produced the gas that lay under the left diaphragm. Did this patient have a perinephritic abscess? From the history, probably not, because he is said to have been well until ten days before admission, and the history of a perinephritic abscess is usually extended. To be sure, spinal curvature is mentioned, and this is sometimes an accompaniment of the muscle spasm related to inflammation about the kidney. We are not told about the ability of the man to extend the leg — nothing about psoas spasm. However, there is such a thing as infection localized in the renal cortex and not communicating with the renal calyxes or pelves, usually beginning rather slowly but eventually extending to the perinephritic tissues. I am thinking especially of the so-called "renal carbuncle." This is about as near as I can come to making a diagnosis: that the patient had a renal carbuncle, which ruptured into the perinephritic tissues, and that an abscess eventually resulted in the production of gas and fluid making it visible on x-ray examination. Of course, that process takes some time, as a rule, and I am surprised, therefore, at the relatively short illness of this patient, but I do not see that this invalidates my diagnosis.

What was the matter with the mastoid process? I have not the remotest idea. What the pain in the neck was due to, I do not know. These things might very easily have been related to a general systemic infection. We are told nothing about blood cultures and given only the story that at some time or other the patient had chills. We are not given his hospital temperature chart. He was operated on, presumably for drainage of this abscess and also for a more accurate diagnosis than it was possible to make before operation.

Dr. Tracy B. Mallory: Here is the chart. The patient did have a fever all the time.

Dr. Quinby: Yes; but this is not a very striking chart.

What happened after the operation, I am not able to say, of course. We are not told that. I should guess that the patient died. I think in all probability he went on to a long suppurative process in the retroperitoneum and upper left quadrant of the abdomen. I do not know, of course, what these air pockets among the small intestines are. If these are related to the abscess, it seems to me that the condition had spread generally throughout the abdomen, and in all probability the operative outlook was bad.

Dr. Mallory: Then your first choice would be carbuncle?

Dr. Quinby: Yes; if you like that term. It is a localized *Staphylococcus aureus* infection of the renal parenchyma and may go on to suppuration outside the renal substance.

Dr. Mallory: When I read over this story, that diagnosis also occurred to me, and I wondered about the bacteriology of so-called "carbuncle of the kidney." If it is due to the staphylococcus, I should not expect to see gas.

Dr. Quinby: The gas was not present all the time; we have a number of x-ray films that do not show it. There may have been secondary invasion by the colon bacillus, a very frequent occurrence.

Dr. Earle M. Chapman: I should like to ask if Dr. Quinby considered the possibility of perforation of the ureter with the catheter at the time the

left retrograde pyelogram was done. The history states that the film was unsatisfactory because of motion. The patient was very active. Is that a possible explanation of the subdiaphragmatic abscess on the left? Does such an accident ever occur?

DR. QUINBY: I do not believe the patient suffered perforation of the ureter by the catheter. That might occur on an attempt to pass a catheter in a ureter adherent or obstructed low in its course, but when 20 cm. of catheter has been introduced, there cannot be enough force exerted to perforate a ureter unless the ureter is already necrotic. That is a possibility, but there is no evidence of it here.

DR. CHAPMAN: I thought the pain in the left neck was explainable as referred pain from diaphragmatic irritation.

DR. QUINBY: I suppose one might have pain in the mastoid process from suppuration under the diaphragm, but it must be rare.

DR. MALLORY: We have seen coronary, and I think pleural, pain referred to that area. It is reassuring to hear the urologist tell us it is almost impossible to perforate the ureter.

DR. J. DELLINGER BARNEY: I have never seen it.

DR. QUINBY: Certainly not high perforation; one cannot exert enough force.

DR. MALLORY: Have you any comment, Dr. Robbins?

DR. ROBBINS: Only that the left kidney is displaced downward by this mass, and I should say from the one retrograde pyelogram film that there is pressure on the upper margin of the pelvis.

DR. GEORGE G. SMITH: The only comment I have is that the story does not quite seem to hang together with the picture. So far as the hematuria goes, it would be a possible accompaniment of infection, but it was a rather unusual amount.

DR. QUINBY: An extrarenal mass making pressure on the renal vein will cause hematuria.

CLINICAL DIAGNOSIS

Subdiaphragmatic abscess.

DR. QUINBY'S DIAGNOSIS

Renal carbuncle of left kidney, with perforation into subdiaphragmatic region, forming abscess containing gas.

ANATOMICAL DIAGNOSIS

Hypernephroma of left kidney, containing colon-bacillus abscess.

PATHOLOGICAL DISCUSSION

DR. MALLORY: There was a great deal of difference of opinion and argument on the service regarding the diagnosis in this case, and eventually, I believe, the patient was transferred from the Urological Service to the Surgical Service on the basis that there was enough chance that the subdiaphragmatic abscess was connected with the gastrointestinal tract to make it wiser to operate from in front rather than from behind.

He was operated on by a general surgeon, and a large tumor mass was found in the kidney area. The mass was removed with some difficulty and proved to be a hypernephroma. In its center was a large cavity in the midst of broken-down and infected tumor tissue, and the gas was all within the hypernephroma. There was no subdiaphragmatic abscess. The patient made an excellent postoperative recovery.

DR. QUINBY: He would not have if the gas had been among the loops of bowel.

CASE 28372

PRESENTATION OF CASE

First admission. A thirteen-year-old schoolboy was first admitted to the hospital because of polyuria and polydipsia.

Two weeks before entry, the patient noticed that he was forced to urinate more frequently than usual, and that he was passing large amounts of urine at each voiding. At the same time, he began to void two or three times each night. He drank at least ten glasses of water a day and seemed hungrier than usual, especially between meals. After several days, he was taken to a physician and found to have sugar in the urine. He was put on a diet and referred to the hospital.

When the patient was two years old, he had a period of "vomiting and malnutrition." At that time, a physician found sugar in the urine. This finding was not followed up. Before the onset of the evident increase in urination, the patient had occasional nocturnal enuresis. Two years before entry, he had scarlet fever, with no symptoms referable to the kidneys. A sister three years younger than the patient had scarlet fever at the age of nine, and was recognized as diabetic at fourteen. Her subsequent course bore a remarkable resemblance to that of the patient. She developed albuminuria after nine years, and retinal hemorrhages and arteriolar narrowing, a blood pressure of 160 systolic, 96 diastolic, edema and a palpable liver after ten years. The patient's father later developed diabetes, hypertension and albuminuria.

On admission, the patient appeared well developed, with evidence of some recent weight loss. The tonsils were enlarged and cryptic, with caseous inclusions. The heart was of normal

size, with a soft systolic murmur at the apex. The abdomen was normal.

The blood pressure was 100 systolic, 65 diastolic. The temperature, pulse and respirations were normal.

Examination of the urine showed 4.5 per cent sugar, no albumin and rare white cells in the sediment. The blood showed a red-cell count of 5,000,000 with 85 per cent hemoglobin, and a white-cell count of 5200 with 66 per cent polymorphonuclears. The blood Wassermann reaction was negative.

The patient was given a special diet, with insulin adjusted to free the urine of sugar. After stabilization, tonsillectomy and adenoidectomy were performed, and he was discharged to the clinic on a maintenance dose of 5 units of insulin a day.

Second admission (ten years later). An acutely inflamed appendix was removed. The patient had continued to be well during this interval, with the insulin varying from 10 to 30 units a day and diet regulation.

Third admission (two years later). The patient, aged twenty-five, had continued in satisfactory health on 40 units of insulin a day. He was readmitted to the hospital because of a cold of three days' duration. The day before re-entry, he took an extra 10 units of insulin because of glycosuria, and subsequently suffered a slight insulin reaction.

On examination, the patient appeared restless, and flushed, with congestion of the conjunctivas and of the nasal mucous membranes.

The blood pressure was 128 systolic, 88 diastolic. The temperature was 100.2°F., the pulse 80, and the respirations 20.

The urine showed a trace of sugar but no albumin or abnormal sediment. The red-cell count was 3,800,000 with 70 per cent hemoglobin and the white-cell count 7000 with 69 per cent polymorphonuclears. The fasting blood sugar was 212 mg. per 100 cc. on the second hospital day. After two weeks, the patient was discharged on 45 units of protamine insulin a day.

Fourth admission (three and a half years later). The patient continued well except for several insulin reactions that necessitated reduction in daily dosage to 40 units of protamine insulin. Two months before re-entry, he changed jobs to do work at irregular night hours. This occasioned difficulty in the adjustment of his meals and insulin. The urine showed sugar in several tests. At about this time, he dropped a heavy weight on his right great toe and later stubbed it. A blister formed near the nail, but soon healed. Five days before re-entry, the toe was stubbed again, and became red in several hours. The next night, the patient had a shaking chill and perspired profusely. He was admitted to the emergency ward of the hospital the next day, where it was found that he had a tender thick callus on the medial aspect of the right great toe, red streaks running up the leg, and tender inguinal lymph nodes. The callus was incised, with release of 2 cc. of pus. The leg was given local heat and elevation. The patient was transferred to the medical ward for readjustment of the insulin dosage.

Examination at this time showed blurring of the disk margin of the right fundus, with marked vascular proliferation over the disk extending into the vitreous. Many small retinal hemorrhages were present. The left eye showed a similar but less advanced picture. The chest was normal. The liver edge was displaced three fingerbreadths below the costal margin on deep respiration. The dorsalis pedis and posterior tibial arteries were palpable. The infection of the right great toe and the accompanying lymphangitis had subsided.

The blood pressure was 130 systolic, 100 diastolic. The temperature, pulse and respirations were normal.

The urine showed a +++ test for albumin in four out of five examinations, traces of sugar, and occasional red and white cells and a few fine granular casts in the sediment. The blood counts were essentially normal. The blood sugar varied from 40 to 120 mg. per 100 cc. The blood cholesterol was 229 mg. per 100 cc.

A roentgenogram of the right foot showed a soft-tissue swelling of the distal phalanx of the great toe, without evidence of osteomyelitis. The vessels appeared calcified.

Cultures of the urine showed *Staphylococcus aureus* and nonhemolytic streptococci. The patient was discharged sugar free on 40 units of protamine insulin a day to attend to some urgent business.

Fifth admission (four days later). The patient returned for further study. Physical examination and routine laboratory studies were as before. The phenolsulfonephthalein excretion was 60 per cent. Urine-concentration tests showed ability to concentrate up to a specific gravity of 1.028. The nonprotein nitrogen varied from 29 to 42 mg. per 100 cc.

A flat film of the abdomen showed well-outlined, slightly enlarged kidneys, with sharp psoas shadows. There was marked calcification of the pelvic arteries. Intravenous pyelograms showed impaired secretion of the dye on the left. Retrograde pyelograms were negative.

No changes were visualized by cystoscopy. Urine from the left kidney showed an occasional white

cell, and gave a moderate growth of colon bacilli. Urine from the right kidney showed 300 red cells per high-power field, with an occasional white cell, and was sterile on culture. Following a moderate reaction to the cystoscopy, the patient was given a course of sulfathiazole. After a week, urine cultures grew nonhemolytic streptococci. After three weeks, the patient again left the hospital for business reasons.

Sixth admission (five days later). The patient returned to the hospital for continuance of studies. Physical examination and routine laboratory studies were essentially as before. Cystoscopy was again performed. The urine obtained from both kidneys was clear. That from the left kidney gave abundant growth of colon bacilli. The phenolsulfonephthalein appearance time was 3 minutes for the left kidney and 4 minutes for the right, with good concentration of the dye on each side. The patient was discharged after a week, on his usual routine.

Seventh admission (one year later). The patient continued to be fairly well, although lacking ambition and strength. He noted that his urine was "cloudy." Three days before entry, there was a sudden onset of sharp pain in the right flank, followed or accompanied by a shaking chill, with a temperature of 101°F. The pain did not radiate, and soon subsided. The night before re-entry, a similar sequence of pain, chill and fever occurred.

Physical examination was as before except for the presence of tenderness in the right flank and costovertebral angle. The pulse, temperature and respirations were normal.

The urine showed a +++ test for albumin, with 10 red cells and 25 white cells per high-power field and with occasional coarse granular casts. Abundant growth of colon bacilli was obtained on culture.

The patient was given sulfathiazole for two weeks. The urine became sterile and cleared except for a few red cells and persistent albuminuria. On discharge, the patient remained on his usual insulin.

Eighth admission (one year later). Three months after discharge, the patient gradually lost central vision in the right eye because of increasing opacity of the vitreous. He continued at work. Five months before re-entry, he began to note edema of the legs and nocturia. The blood pressure was found in the clinic to be 190 systolic, 110 diastolic. Ammonium chloride was prescribed, but was soon discontinued because of indigestion. Gradually, exertional dyspnea appeared, with puffiness of the eyes. A month before re-entry, headaches were noted, centering over the right eye. Following an upper respiratory infection, generalized aches and pains developed. In the two weeks before re-entry, vision began to fail in the left eye. The patient suffered almost constant severe frontal headaches, vomiting and edema of the eyes and legs. At the time of entry, he was thirty years old.

Examination showed a pale, chronically ill man with edema of the face, sacrum and lower extremities. Vision was limited to finger counting at twelve inches. The heart was at the upper limits of normal size, with sounds of good quality and regular rhythm; the aortic second sound was greater than the pulmonic. The lung fields were clear. The abdomen showed questionable evidence of free fluid. There was moderate tenderness in the right costovertebral angle.

The blood pressure was 210 systolic, 130 diastolic. The temperature, pulse and respiration were normal.

The urine showed a ++++ test for albumin, a trace of sugar and a specific gravity of 1.010, with occasional red and white cells and hyaline and granular casts. The red-cell count was 3,400,000 with 11.2 gm. hemoglobin, and the white-cell count 13,200. The nonprotein nitrogen was 45 mg. and the serum protein 4.1 gm. per 100 cc. The carbon dioxide combining power was 23.4 milliequiv. and the chlorides 104.2 milliequiv. per liter. The calcium was 10.6 mg., the phosphorus 4.2 mg., and the phosphatase 4.1 Bodansky units per 100 cc.

Intravenous pyelograms showed no definite excretion of dye in the course of an hour.

The patient did poorly. There was frequent vomiting, and the peripheral edema persisted. A furuncle slowly developed on the right leg. It was poulticed at first, and later incised and drained. The patient was discharged slightly improved after five weeks.

Final admission (two days later). The patient remained in bed at home. At 2 o'clock in the morning of the day of re-entry, he had a brief generalized convulsion. He was then rational for three hours, when he became unresponsive except to painful stimuli, and had frequent generalized convulsions. He had taken the usual dose of 20 units of protamine insulin on the preceding day.

On examination, the skin was hot and dry. The eyeballs were firm and roving. The heart action was rapid and regular, with a scratchy sound heard only during systole and limited to the pulmonic area. The lungs seemed clear. The bladder was distended to two fingerbreadths above the umbilicus. Tendon reflexes were active, with bilateral Babinski plantar responses.

The blood pressure was 260 systolic, 150 diastolic. The temperature was 104°F., the pulse 140, and the respirations 35.

Examination of the urine was as before. The white-cell count was 42,000 with 97 per cent polymorphonuclears. The blood sugar was 1047 mg. per 100 cc., falling to 731 mg. in two hours, after administration of 30 units of protamine insulin and 66 units of ordinary insulin. The carbon dioxide combining power was 17 milliequiv. per liter. A lumbar puncture gave clear fluid under an initial pressure of 230 mm. of water.

Consciousness was never regained. The fever remained high. Therapy included 500 cc. of 2 per cent magnesium sulfate solution, and repeated doses of insulin. Death occurred on the second hospital day.

Differential Diagnosis

Dr. Thomas V. Urmy: I think we all agree that this man had diabetes mellitus, and that it probably began much earlier than at the age of thirteen. He may have had it at two. At no point until the end was there any great difficulty in controlling the glycosuria. One would have to say that this was not more than a moderately severe case.

Probably the most striking feature in the whole history is the story that the younger sister and father developed very similar clinical pictures. It immediately raises the question whether or not we are encountering a definite syndrome or pathologic entity characterized by diabetes, renal lesions and vascular changes instead of a mere coincidence of separate diseases. Such a syndrome has been described in the past few years, although in what little reading I have done, I do not remember any account of family predisposition. This newly recognized disease has been called intercapillary glomerulosclerosis. Its clinical manifestations have been diabetes, hypertension, albuminuria and retinal vascular changes. The albuminuria and retinal changes have usually been rather marked, particularly the latter which are out of proportion to the appreciable length of time most of these people survive discovery of the condition. Edema is another common finding and often reaches a degree suggesting nephrosis. Thus, this patient's story can be explained by this condition, although we should possibly consider some other things.

Ordinarily, we should have to rule out chronic glomerulonephritis, with a nephrotic element terminally. It is rather difficult to do this clinically. The patient gave a history of what appears to have been a streptococcal infection at the time of his fourth admission, when he was twenty-six and a half years old. At the same admission, it was found that he had slight hypertension, as well as some albumin and casts in the urine. The peculiar feature then was that he already had marked vascular changes in the retinas. It is difficult to believe that such changes could have progressed so far since the onset of the streptococcal infection. We also have a history consistent with recurrent urinary-tract infections. On one entry, it appears that the patient must have had pyelonephritis. Therefore, I wonder if this contributed to his evident renal failure.

Of course, hypertension is very much commoner in diabetes than in the general population. Was this, simply, hypertension developing in a patient with diabetes since an early age? Early x-ray studies reported here did show marked arteriosclerotic changes. One must also consider kidney failure developing secondary to hypertension, with later a nephrotic picture due to a possibly coincident amyloid disease.

I think, as I have said, that it is difficult to rule out completely the other possibilities, but there are certain things that make it more likely that the condition of intercapillary glomerulosclerosis was present. One is the relatively long survival — two years — after marked retinal changes were demonstrated. The serum protein was very low. Probably, there was more albuminuria than is seen in the ordinary case of chronic glomerulonephritis. Edema was more prominent, too.

Against the diagnosis is the age of the patient. I have not reviewed all the cases reported, but in a series that Newburger and Peters[1] reviewed in 1939, all patients were in older age groups. The youngest one did not develop even diabetes until after the age of forty. It seems quite unusual to have the diabetes begin so early in childhood and to have the whole course of the disease completed before the age of forty. The sex is also somewhat against this diagnosis, since the condition is described as much commoner in females than in males. The family history is, to my knowledge, unusual. However, I do not believe that these inconsistencies overbalance the points in favor of intercapillary glomerulosclerosis.

Dr. Allen G. Brailey: A number of cases in childhood have been reported. I cannot give the reference, but I recall reading it recently.

Dr. Tracy B. Mallory: Dr. Beckman, you have seen a case at a comparatively early age.

Dr. W. W. Beckman: Yes; it started in a person with diabetes from childhood. The patient, slightly over thirty, is still alive, with such severe retinal changes that he is almost completely blind.

All the other features are the same, — diabetes and so forth, — and he has a uremia that is not causing much trouble.

Clinical Diagnoses

Diabetes mellitus.
Intercapillary glomerulosclerosis.
Vascular nephritis?
Uremia.
Hypertensive encephalopathy?

Dr. Urmy's Diagnosis

Intercapillary glomerulosclerosis.

Anatomical Diagnoses

Intercapillary glomerulosclerosis, chronic, advanced.
(Diabetes mellitus.)
(Uremia.)
Cerebral edema.
Pulmonary edema.
Arteriosclerosis, marked, coronary and renal.
Cardiac hypertrophy, hypertensive type, slight.
Cardiac dilatation, slight.

Pathological Discussion

Dr. Mallory: About six years ago, Kimmelstiel and Wilson,[2] who at that time were working at the Boston City Hospital, were set to work by Drs. Frederic Parker, Jr., and Soma Weiss on a group of hypertensive cases. They made an extensive clinicopathological survey of a large group of hypertensive patients, in the course of which they found nothing very dramatically new regarding hypertension, but of that group of cases they recognized that a small number showed a different picture, both clinically and histologically, from all the rest. All turned out to be diabetic patients, and all had a peculiar lesion in the kidney, predominantly shown in the glomeruli. Their description went unnoticed for several years, and then Dr. Peters and others took it up and began to find clinical cases in considerable numbers. As so often happens, when attention is called to a disease, one begins to see it, and what one first thinks is quite rare he soon discovers is comparatively common. We have now seen a number of cases, and we have another case very much like this one, with diabetes starting in childhood and with hypertension and the rest of the symptoms developing rather suddenly some twelve years later.

Microscopically, the renal lesions are quite characteristic. There is partial to complete hyalinization of the glomeruli, and the atrophied tubules are characteristically surrounded by extensive deposits of some peculiar hyaline material. The glomeruli are hyaline, acellular masses, which tend to occupy the central portion of each of the loops of the tuft. From the point of view of histologic diagnosis, I think the most characteristic finding is the way in which each of the hyaline masses is surrounded by a group of apparently normal capillaries. In the ordinary case of glomerular or vascular nephritis, hyalinization of the glomeruli is, of course, common, but when as much hyalinization as this occurs in either of those other conditions, the normal capillaries are not so numerous at the periphery.

The kidneys grossly were a little larger than normal, weighing 400 gm., whereas a chronic glomerulonephritis of this duration would certainly be associated with shrunken and contracted kidneys. In all the cases we have seen of intercapillary glomerulosclerosis, the kidneys were of normal or slightly increased size and not contracted. There were a few foci in these kidneys of definite inactive, healed pyelonephritis, but these changes were overshadowed by those characteristic of Kimmelstiel–Wilson disease.

There was no other very important finding at autopsy. We found nothing to explain the terminal dramatic episode except a moderate degree of cerebral edema, with a little pressure cone. I think the terminal episode was essentially uremia.

Dr. Beckman: How about a hypertensive encephalopathy?

Dr. Mallory: I suppose that is possible. I do not know how to distinguish it anatomically.

Dr. Reed Harwood: Did the patient have pericarditis?

Dr. Mallory: No. We looked very carefully, because someone came to the autopsy who had heard a pericardial friction rub and asked us to search for evidence of pericarditis, but it was not there.

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FINANCIAL AID TO NEEDY MEDICAL STUDENTS

The accelerated program of medical education adopted by nearly 90 per cent of the medical schools in the United States has resulted in a marked lowering of the opportunities for needy students to earn money for support during their periods of study. In the April issue of *Pulse*, the official publication of the New England Section of the Association of Internes and Medical Students, it was estimated that the students of four medical schools in Greater Boston annually earn over $100,000, and for the greater part of this sum to be denied would undoubtedly mean financial hardship to many.

The difficulty is being met in a variety of ways. In the first place, a three-year schedule means a lowering of the ordinary costs of the student—travel, board, lodging and so forth. Secondly, certain educational institutions that conduct medical schools are diverting a larger proportion of their loan and scholarship funds to assist these graduate students, who are so vital to the health and the defense of the Nation. And, finally, money for loan funds has been made available by philanthropic organizations and by the federal government—a fact that merits special attention.

The W. K. Kellogg Foundation has offered $10,000 to every approved medical school in the United States and to certain dental and nursing schools, and the Charles H. Hood Educational Trust has established grants to the three approved medical schools in Boston; these sums may be used for scholarships and loans to deserving and needy students. Furthermore, Congress has recently appropriated $5,000,000 for the use, in accordance with regulations promulgated by the United States Office of Education, with the approval of the chairman of the War Manpower Commission, of students in the fields of medicine, dentistry, pharmacy, chemistry, physics and engineering. Such loans are to be limited to tuition and fees, plus $25 a month, the total loan for any student not to exceed $500 annually. The student must be participating in an accelerated program that can be completed in two years. The interest charge will be 2½ per cent, and the loans are to be canceled if the borrower, before completing his course, is ordered into military service under the Selective Training and Service Act or if he is permanently disabled or killed.

With these provisions, there is little likelihood that prospective physicians will be forced to discontinue their educational programs.

COMMUNICABLE DISEASES IN WARTIME

Physicians interested in military medicine are well aware of the importance of infectious and communicable diseases in the conduct of warfare. From recent history can be cited examples of typhoid and other enteric fevers during the Spanish-American War and the various communicable

diseases, notably the respiratory infections, including influenza, in World War I. In each of these two wars, there were more deaths and more man-days of service lost on account of infectious diseases than were attributable to all forms of battle injuries. Zinsser memorialized the place of typhus fever in determining the course of wars in Central Europe in his book, *Rats, Lice and History*. He also emphasized the experience of the United States Army in the last war, which indicated that the major single factor in the speed with which respiratory infections spread in army camps was the rapid concentration of raw recruits, a warning that apparently has been very much heeded in the building up of military forces in the present emergency.

The significance of communicable diseases in warfare has been recently reviewed by Dr. W. C. Davison,[1] of Duke University. In relation to military establishments, this well-known pediatrician and educator also points out certain aspects of the carrier problem that require careful and intelligent consideration. Obviously, widespread search for such pathogenic organisms as meningococci, diphtheria bacilli, hemolytic streptococci and pneumococci among troops, especially when cases of acute infections due to these organisms begin to appear, will reveal large numbers of healthy carriers both among contacts of cases and among persons without contact. To isolate such carriers and thus remove them from training and active duty might have an unfavorable psychologic influence on the men, and — what is of more consequence — it results in a considerable waste of valuable man-days of training or of combat. This should, of course, be avoided, so far as possible, or measures should be adopted that would cope with the carrier problem in such a way as not to interfere with routine duties.

Davison points out the desirability, if not the necessity, of having men trained in the management of communicable diseases to cope with such problems, which invariably arise when young men are brought together in large numbers. Since the significant communicable diseases are for the most part children's diseases, he stresses the role of the pediatrician in this field. In addition, public-health workers, medical bacteriologists and internists who are experienced in the management of infectious diseases all have special training that equips them to handle these problems, both in the armed forces and in civilian communities, and it is there that such persons can best serve in this all-out war.

Waldemar Kaempffert,[2] in his science column, expresses the belief that Davison has exaggerated the seriousness of infectious diseases in wartime. He points to the freedom from major epidemics in many of the countries now at war. Unfortunately, accurate reports of medical conditions in the warring nations are not available, whereas Davison's remarks are based on accurate data accumulated during World War I. It is certain, however, that much of the reduction in the incidence of preventable infections over previous figures in the various military forces now engaged in the war, if such a reduction has actually occurred, is the result of well-organized and well-executed programs of vaccination and sanitary control. It may be well to contemplate the adoption of intelligent programs to extend prophylactic vaccination and education of the population at large in an attempt to diminish the effects of preventable infections among civilians.

References

1. Davison, W. C. Reduction of communicable diseases among troops and children during national defense program. *War Med.* 1:863-872, 1941.
2. Kaempffert, W. Science in the news: disease and war. *New York Times* December 14, 1941.

MEDICAL EPONYM

Dorothy Reed Cells

These cells were described by Dr. Dorothy M. Reed, then fellow in pathology at Johns Hopkins University, in a paper, "On the Pathological Changes in Hodgkin's Disease, with Especial Reference to Its Relation to Tuberculosis," which appeared in the *Johns Hopkins Hospital Reports* (**10**:133–196, 1902). A portion of the text follows:

> The *large giant cells*, which are the most striking features of these specimens, are evidently formed from . . . proliferating "endothelial" cells. Transitions from epithelioid cells to large uninuclear cells, and from these to giant cells with one or more nuclei can easily be found. These giant cells usually lie free in the

interstices of the tissue, but we occasionally see them on the reticulum, and with irregular protoplasmic processes. They occur in great number in the large lymph sinuses of the gland, and occasionally appear in the blood-vessels. They vary from the size of two or three red blood corpuscles to cells twenty times this size. . . . These giant cells, so far as our observation reaches, are peculiar to this growth, and are of great assistance in diagnosis.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

CASE HISTORY: FATAL PERNICIOUS VOMITING

A twenty-four-year-old Italian multipara, approximately six weeks pregnant, entered the hospital because of nausea and vomiting. The past history was irrelevant, with no contagious diseases or surgical operations. She had had two previous pregnancies, both of which were normal; the children were living. On entry, the patient was reported to have had a high degree of acetone and the slightest possible trace of albumin in the urine; she stayed in the hospital for about two weeks. The treatment, which was probably medical, resulted in improvement, and she was discharged relieved. Two days after discharge, vomiting recurred, and she summoned another physician. The vomiting had increased to such an extent two days later that hospitalization was again recommended but was refused; instead, the patient was seen daily at home by the physician but was said to be generally unco-operative. She was said to have shown improvement for a week or ten days, when she was not seen professionally, but at the end of this time, when she was approximately three months pregnant, vomiting again recurred in an exaggerated form. Hospitalization was advised but once more was refused. A week later, the patient was seen by another physician; she was moribund and died the following day.

Comment. This case is reported to show that pernicious vomiting may still be fatal. Although medical advice was given, it was not followed, and this fatality can be attributed solely to the ignorance and obstinacy of the patient. Whether therapeutic abortion was suggested is not known, but this last resort is rarely necessary if a patient is willing to be hospitalized. Rest in bed, intravenous glucose solution, thiamine chloride and mild sedatives almost always give relief if the acidosis has not reached the point of liver destruction.

DEATH

JACKSON — OLIVER H. JACKSON, M.D., of Fall River, died June 1. He was in his seventy-first year.

Born in Auburn, Maine, Dr. Jackson received his degree from Long Island College of Medicine in 1894. He was a member of the American Laryngological, Rhinological and Otological Society, the New England Ophthalmological Society and the New England Otological and Laryngological Society, and was a fellow of the American College of Surgeons, the Massachusetts Medical Society and the American Medical Association.

His widow, two sons and a daughter survive him.

WAR ACTIVITIES

CIVILIAN DEFENSE

CONSERVATION OF DEALERS' STOCKS OF MEDICAL AND SURGICAL SUPPLIES

The following statement was recently forwarded by the United States Office of Civilian Defense, Washington, D. C., to all state chiefs of Emergency Medical Service, with a request that they transmit it to local chiefs of Emergency Medical Service and to hospitals and state and local medical societies:

> The medical profession and the hospitals of the Nation will shortly be obliged to depend on dealers' stocks of medical and hospital supplies if they are to maintain their present level of efficiency. The continued shortage of raw materials makes it increasingly evident that even the armed forces may have difficulty in securing their requirements. Stocks on the shelves of the dealers of this nation constitute the only reserve of medical and hospital equipment that will be available in the near future to meet civilian needs. The hoarding and dead storage of equipment and supplies for a possible emergency should therefore be discouraged. Any unexpected emergency can be met by our present civilian medical and hospital resources; continued disaster can only be met by the utilization of military stores, which would be made available if there were urgent need.
>
> Any surplus or obsolete equipment now in the possession of physicians and hospitals ought not to be dispersed at this time, because of the difficulty of replacement and the possibility that it may be needed for the establishment of emergency base hospitals.

CORRESPONDENCE

ENLISTMENT IN NAVAL RESERVE

To the Editor: According to recent information from the Navy Department, physicians may immediately enlist as apprentice seamen in the Naval Reserve in an inactive status. The fact that they have made, or are making, application for commissions in the Medical Corps of the Naval Reserve does not bar their eligibility for this enlistment. If and when commissions are received, transfers will be effected from the enlisted status to that of a commissioned officer in the Medical Corps, and active-duty orders should be expected immediately.

There are, no doubt, a number of prospective naval medical officers who will be particularly interested in this new ruling. I should like to remind the profession that commissions are available up to the age of fifty.

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Naval Officer Procurement
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RHUS TOXIN

To the Editor: Today, I saw a man with an urticarial type of skin eruption. His local physician, who referred him, had said that he had poison-ivy dermatitis and that, to save time, he might as well receive an injection of rhus toxin. The physician also stated that the toxin was a specific for poison-ivy dermatitis and that, even if he did not have this type of eruption, the injection would do him no harm.

I believe this false sense of security prevails among the medical profession at large, owing to the enthusiasm of detail men from the various drug houses. If this physician were to attend any large dermatologic clinic, practice dermatology or give injections of this antigen to a large series of patients, I am sure that he would be convinced that his statement was not true. These injections do a great deal of harm in many cases.

For example, within the past week I have seen at least ten bad results from them. One patient received an injection in the arm, with a resulting erythema and edema that was very disabling and painful. Another patient received a series of injections, and six days after the last, when the dermatitis had healed, was seized with a severe urticarial reaction that persisted for a considerable length of time. Still another patient had a widespread attack of what was formerly called "chronic eczema" but is now labeled "neurodermatitis." It came on three weeks after a series of injections with rhus antigen. This neurodermatitis is probably the beginning of a disabling dermatitis, which will prevent the patient, a student nurse, from completing her training.

I have also seen cases of exfoliative dermatitis occurring after this type of injection.

Rhus toxin cannot be given without the ever-present danger of a later allergic reaction. It should be used with caution. I have found it to be of little value in therapy, and its use as a prophylactic is still being disputed by many dermatologists.

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REPORT OF MEETING

BOSTON CITY HOSPITAL

The second in the series of lectures sponsored by the Boston City Hospital House Officers' Association for the preparation of those entering the armed forces was held at the hospital on May 7, with Dr. Henry Marble discussing "Traumatic Surgery."

Two of the most trying problems of the World War I have been minimized by the routine blood typing of all men and the administration of tetanus toxoid for active immunization.

The first-aid treatment of fractures of the extremities has not changed much. Some type of Thomas splint for all fractures between the ankle and hip or of the Murray-Jones splint for those between the wrist and shoulder is still the immobilization of choice. The only things that need be emphasized are the use of adequate padding and the keeping on of the splint for the shortest possible period. In compound wounds, iodine is painted around the skin edges only, and a dry sterile dressing applied. Most, if not all, men in combat will be supplied with some sulfonamide powder, at least 1 gm. of which should be inserted in such wounds. The patient should be treated for shock, with double the usual amounts of morphine, warmth and adequate splinting, and for incipient sepsis with sulfonamide orally.

The first-aid station or field hospital is essentially a "triage station," where the patients are segregated into shock cases, chest wounds, abdominal wounds, minor wounds and so forth. An experienced man does this important phase of the work. The order of operations is generally abdominal, chest, head and extremities. All cases of actual or incipient shock are treated in special rooms with plasma or blood, as well as the usual supportive measures.

Dr. Marble discussed particularly wounds of the extremities, which are usually not considered emergencies. Some amputations, which are performed at the field hospital, are of the guillotine type. It is definitely established that the use of the sulfonamides at the first-aid station lengthens to as long as seventy-two hours the period in which a wound may be treated as fresh and a primary débridement done. Anesthesia is a difficult problem largely because of transportation limitations. Ether is bulky and explosive, and nitrous oxide is also bulky. Spinal anesthesia is fine for the lower extremities if available, and Pentothal is satisfactory in the arm. Both, but particularly the latter, require what probably is not generally available — an experienced and competent anesthetist. This all indicates that chloroform, which is infinitely easier to transport, will be in wide use. Its dangers, furthermore, are probably overemphasized, according to Dr. Marble.

The first consideration, of course, is an evaluation of the case for shock and continuance of its treatment. Compound wounds are débrided and copiously irrigated. But, here again, what is written in the books may often not materialize because of lack of the "sharp knife and unlimited quantities of sterile fluid." The best must be done, often with inferior equipment. Again the wound is dusted with one of the sulfonamides, which is also given by mouth. The wounds are left open, despite the fact that they are now being closed by some men even in the presence of gas bacilli when the sulfonamides are used. This is not yet practical on a large scale. The number and virulence of gas bacilli vary remarkably with the locality.

The fracture itself at the field hospital is best returned to its traction splint, possibly with skin traction instead of the ankle or wrist hitch. Further transportation is in the offing, and the use of plaster-of-Paris casts has not proved practical when the state of the wound is questionable, and when constant observation during transport is not possible. When good results have been reported with this method, the wounds have been fresh, and there has been no further transportation. If adhesive skin traction has been instituted, the patient is always ready for transfer to bed traction. In Dr. Marble's opinion, closure of wounds is permissible only when they have been proved bacteriologically to be reasonably free of at least serious pathogenic organisms. Such facilities are usually found only at base hospitals farther back. Plating of fractures may be carried out in the rare event that the equipment is at hand, but even then the wound should be left open.

Whenever severed nerves are encountered, an attempt should be made at a suture of some sort. It has been demonstrated that these structures do almost as well in septic as in clean wounds, and any identifying material on the nerve ends facilitates secondary repair of the nerve. For this reason, some means of identification should always be introduced, for improperly treated nerve injuries result in the severest sequelae.

Tendons, on the other hand, have notoriously poor results in septic areas. But this should not prevent one from attempting suture, for nothing is lost and the ends may be kept somewhere near approximation for secondary repair. In any event, Dr. Marble is not yet ready to advocate primary closure of the superficial tissues in compound wounds of any kind.

(Notices on page x)